Evidence Report

Cardiovascular Disease and Commercial Motor Vehicle Driver Safety (Expedited Review)

Presented to

Federal Motor Carrier Safety Administration

April 27, 2007

Prepared for

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This report is comprised of research conducted to analyze the impact of Cardiovascular Disease on Commercial Motor Vehicle Driver Safety. Federal Motor Carrier Safety Administration considers evidence, expert recommendations, and other data, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and regulatory processes.

Policy Statement

This report was prepared by ECRI under subcontract to MANILA Consulting Group, Inc., which holds prime Contract No. GS-10F-0177N/DTMC75-06-F-00039 with the Department of Transportation's Federal Motor Carrier Safety Administration (FMCSA). ECRI is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI has been designated an Evidence-based Practice Center by the United States Agency for Healthcare Research and Quality. ECRI's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information regarding the current state of knowledge on this topic. It is not intended as instruction for medical practice, or for making decisions regarding individual patients.

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Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12% of all worker deaths. About two-thirds of workers killed in the trucking industry are the consequence of highway crashes. According to statistics from the United States Department of Transportation, there were 4,932 fatal crashes involving a large truck in 2005 for a total of 5,212 fatalities. In addition, there were 137,144 nonfatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by the Federal Motor Carrier Safety Administration (FMCSA). Each of these key questions was developed by FMCSA so that the questions' answers would provide information that would be useful in updating its current medical examination guidelines titled, "Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Drivers."(1) The six key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with cardiovascular disease (CVD) at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What are the risk factors for rupture of an aortic (abdominal or thoracic) aneurysm?

Key Question 3: Is implantation of a pacemaker effective in preventing vasovagal syncope recurrence?

Key Question 4: What is the risk of sudden incapacitation or sudden death following implantation of an implantable cardioverter defibrillator (ICD)?

Key Question 5: What is the risk of sudden death or incapacitation in individuals with low left ventricular ejection fraction (LVEF) (<50%, <40%, <35%)?

Key Question 6: Is the relationship between LVEF and sudden death or incapacitation (if established) dependent on the underlying etiology of heart failure?

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this report were identified using a process consisting of several factors. They included a comprehensive search of the literature, an examination of abstracts of identified studies in order to determine which articles would be retrieved, and the selection of the actual articles that would be included in each evidence base.

A total of seven electronic databases (Medline, PubMed (preMEDLINE), EMBASE, PSYCHInfo, CINAHL, TRIS, and the Cochrane Library) were searched (through November 28, 2006). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant ones not identified by our electronic searches. Hand searches of the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori*.

Grading the Strength of Evidence

Our assessment of the quality of evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question; we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. Random- and fixed-effects meta-analyses were used to pool data from different studies.(2-6) Differences in the studies' findings (heterogeneity) were identified using the Q-statistic and I^2.(7-9) Sensitivity analyses, aimed at testing the robustness of our findings, included the use of cumulative fixed- and random-effects meta-analysies.(10-12) The presence of publication bias was tested for using the "trim and fill" method.(13-15)

Presentation of Findings

In presenting our findings we made a clear distinction between qualitative and quantitative conclusions, and we assigned a separate strength-of-evidence rating to each conclusion format. The strength-of-evidence ratings assigned to these different types of conclusions is defined in Table 1.

Table 1. Strength-of-Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect-Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

Evidence-based Conclusions

Key Question 1: Are individuals with CVD[1] at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

A number of conclusions can be drawn from the findings of the analyses of the evidence pertaining to Key Question 1. These conclusions are presented below:

[1] With an emphasis on crash risk associated with myocardial infarction, angina pectoris, coronary insufficiency and thrombosis

Drivers of Commercial Motor Vehicles (CMVs)

1. **A paucity of data from studies that enrolled CMV drivers with CVD precludes one from determining whether CMV drivers with the disorder are at an increased risk for a crash.**

   Two studies presented data directly relevant to the question of whether CVD has an impact on CMV driver safety.(16,17) Medgyesi et al.(16) (Quality Rating: Low) presented crash data for drivers with Class 1 through 4 licenses (comparable to U.S. CMV drivers) separately from Class 5 license holders (private motor vehicle drivers). However, we were precluded from calculating an estimate of the risk ratio for this study, because crash data for the controls with Class 1 though Class 4 licenses were not presented. Only crash data for the entire control group (Class 1 through Class 5) was presented, and this group was dominated by Class 4 license holders. Thus, useful evidence on the relationship between CVD and crash risk among CMV drivers is limited to the findings of just one study.

   Dionne et al.(17) estimated the effects of different medical conditions on truck driver crash risk using data from a nested case-control study (Quality Rating: Moderate). These investigators did not find evidence supporting the contention that CMV drivers with CVD are at an increased risk for a crash. While these results are interesting, the study is not of high quality and its results have not been replicated. Consequently, an evidence-based conclusion pertaining to whether CMV drivers with CVD are at an increased risk for a motor vehicle crash is not drawn at this time.

Drivers of Non-CMVs

Because data from studies of CMV drivers with CVD are scarce, we deemed it worthwhile to examine relevant data from studies that investigated crash risk associated with CVD among more general driver populations. While the generalizability of the findings of these studies to CMV drivers may not be clear, such findings—do at the very least—provide the opportunity to draw evidence-based conclusions about the relationship between CVD and motor vehicle crash risk in general.

The findings of our analyses of crash data from these studies are summarized in Table 2.

Table 2. Summary of Findings

CVD	RR studies	Strength of Evidence Stability of SES	OR studies	Strength of Evidence Stability of SES

Any	Increased crash risk RR = 1.43 (95% CI: 1.11–1.84)	Strength of Evidence: Acceptable Stability of Estimate: Low	No evidence-based conclusion	Unacceptable
Hypertension	Increased crash risk RR = NP	Strength of Evidence: Acceptable Stability of Estimate: Unstable	No evidence-based conclusion	Unacceptable
Arrhythmia	No evidence-based conclusion	Unacceptable	No evidence-based conclusion	Unacceptable
Coronary Artery Disease	No evidence-based conclusion	Unacceptable	No evidence-based conclusion	Unacceptable
Other	No evidence-based conclusion	Unacceptable	No evidence-based conclusion	Unacceptable

CI Confidence interval.
NA Not applicable.
NP Not presented.
OR Odds ratio.
RR Rate ratio.
SES Summary effect size (summary estimate of RR).

The evidence-based conclusions that we draw from the findings summarized above are as follows:

1. **As a group, drivers with CVD are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Acceptable).**

   - **The magnitude of this increased risk is small but statistically significant (RR = 1.45, 95% CI: 1.11–1.84). In other words, the crash risk for an individual with CVD is 1.43 times greater than for a comparable individual who does not have the condition (Stability of Estimate: Low).**

   Eight studies (Median Quality Rating: Low) reported data on the relative incidence of crash among individuals who have CVD (any type) and comparable individuals without the disorder. The findings of the eight studies were quantitatively consistent. Pooling of the data found that the crash rate ratio associated with CVD is 1.43 (95% CI: 1.11 to 1.84). Thus, if the underlying crash risk for a CMV driver is 0.08 crashes per person each year, the crash risk for a CMV driver with CVD will be approximately 0.11 crashes per person each year. Although a series of sensitivity analyses found this estimate to be robust, the strength of our conclusion must be tempered by the fact that the studies providing the data used to produce this estimate were of low methodologic quality. In addition, the fact that the crash data used in our analyses did not pertain to CMV drivers may further limit the value of our findings. The reason for this is because the generalizability of our findings to this population of drivers is unknown.

2. **Drivers with hypertension are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Acceptable).**

    - **The magnitude of this increased risk cannot be determined at the present time.**

    Two included studies (Median Quality Rating: Low) reported on the difference in the incidence of a motor vehicle crash observed among individuals with hypertension and comparable individuals without the disorder. The findings of both studies suggest that individuals with hypertension are at an increased risk for a motor vehicle crash when compared with individuals without the disorder. Because data from only two studies are available, however, we have not pooled their data using meta-analysis in order to obtain a summary estimate of the magnitude of this increased risk.

3. **A paucity of consistent data precludes one from drawing evidence-based conclusions as to whether individuals with coronary artery disease (CAD), arrhythmias, or other types of CVD are at increased risk for a motor vehicle crash.**

Key Question 2: What are the risk factors for rupture of an aortic (abdominal or thoracic) aneurysm?

Specific findings of our assessment of the evidence that addressed Key Question 2 are presented below:

1. **The most commonly observed risk factor for abdominal aortic aneurysm (AAA) is aneurysm size (Strength of Evidence: Moderate).**

    - **Due to the fact that there were a number of methodologic problems involving heterogeneity of the populations studied, biases, statistical power issues, and lack of standardization regarding aneurysm measurement and reporting, no attempt was made to construct a quantitative model describing the risk of rupture for an AAA.**

    Fourteen (Total N = 3,317) moderate-quality studies assessed the potential risk factors for rupture of an AAA. Of these 14 studies, 10 found that aneurysm size was the most important risk factor to be associated with AAA rupture. Other risk factors for AAA rupture that were identified included: chronic obstructive pulmonary disease (COPD) (k = 1 study), presence of hypertension (k = 2 studies), AAA expansion rate (k = 3 studies), smoking status (k = 1 study), aortic wall stress (k = 1 study), aortic

tortuosity (k = 1 study), bronchiectasis (k = 1 study), aortic outpouching (k = 1 study), and female gender (k = 2 studies).

2. **The most commonly observed risk factor for thoracic aortic aneurysm (TAA) rupture is aneurysm size (Strength of Evidence: Acceptable).**

    - **Due to the fact that there were a number of methodologic problems involving heterogeneity of the populations studied, biases, statistical power issues, and lack of standardization regarding aneurysm measurement and reporting, we did not attempt to determine a quantitative model describing the risk of rupture for an aortic aneurysm or TAA.**

    Seven (Total N = 3,908) low-quality studies assessed the potential risk factors for rupture of a TAA. All seven studies found that aneurysm size was the most important risk factor associated with aneurysm rupture. Other risk factors identified for TAA rupture included age, presence of uncharacteristic chronic pain, and COPD.

Key Question 3: Is implantation of a pacemaker effective in preventing vasovagal syncope recurrence?

Our assessment of the evidence that addressed Key Question 3 is presented below:

1. **The Best available evidence does not support the contention that permanent, implanted dual-chamber pacemakers are effective in reducing the recurrence of vasovagal syncope in individuals with high recurrence rates (Strength of Evidence: Moderate).**

    - **Because of inconsistencies in the findings of the studies that comprise the evidence base for Key Question 3, we refrain from providing a single estimate of treatment effect at this time.**

    Five moderate-to-high quality randomized controlled trials (RCTs) addressed Key Question 3. Outcomes assessed by all five studies included the proportion of individuals experiencing recurrent syncope, the time to recurrence, and adverse events.

    Analysis of these data found that the results of the high-quality (k = 2) and moderate-quality (k = 3) studies differed significantly. All three moderate-quality studies found that permanent dual-chamber pacemakers significantly reduce the number of recurrences of vasovagal syncope when compared to standard

treatment. However, neither of the two high-quality studies found evidence to support the contention that permanent dual-chamber pacemakers offer an effective treatment option for individuals with recurrent syncope. The difference in findings may be attributed to a lack of blinding in the three moderate-quality studies in a group of individuals who are known to respond strongly to placebo.

Key Question 4: What is the risk of sudden incapacitation or sudden death following implantation of an ICD?

Specific findings of our assessment of the evidence that addressed Key Question 4 are presented below:

1. **Whether individuals with an ICD implant experience crash that can be directly attributed to CVD or the ICD implant itself cannot be determined at the present time.**

   Four of six included studies presented data on the number or frequency of crashes that occurred among individuals with an ICD. None of these studies compared crash rates occurring among individuals with an ICD to crash rates among individuals either without and active ICD or without CVD. Consequently, it is not possible to determine whether individuals with an ICD are at increased risk for a motor vehicle crash.

   Crashes reportedly occurred among individuals enrolled in only one of the four included studies. Eleven individuals enrolled in this study experienced at least one crash during follow-up. Of these, only one was reportedly the fault of the driver, and this crash was not the consequence of either CVD or an event associated with the implanted ICD. The fact that no crashes reportedly occurred in the remaining studies may be the combined consequence of the small size of these studies and their short follow-up times. In order to determine a reliable crash rate estimate among individuals with ICDs, studies with far larger sample sizes and longer follow-up times are needed.

2. **Whether individuals with an ICD implant experience sudden death or incapacitation during driving cannot be determined at the present time.**

   Three of six included studies reported on occurrence rates for syncope and sudden death among individuals with an ICD while they were driving. None of the individuals enrolled in these three studies experienced syncope or sudden-cardiac death (SCD) while driving. Because syncope and sudden death are rare events, the fact that no cases were observed in the three included studies cannot be

considered as evidence that such events will not occur while driving. In order to determine reliable estimates of these rates among individuals with ICDs, studies with far larger sample sizes and longer follow-up times are needed.

3. **Some individuals with ICD will experience ICD discharge while they are driving (Strength of Evidence: Strong).**

    - **Quantitative assessment of the available data suggests that approximately 6.3% (95% CI: 4.7–8.4%) of individuals who drive with an ICD will experience an ICD discharge while driving (Stability of Estimate: Low).**

      All six included studies reported on the occurrence of ICD discharge during driving. Five of these six studies reported that ICD discharge while driving did occur in some individuals. Despite the fact that follow-up times varied across studies, data on the proportion of individuals who experienced ICD discharge while driving were remarkably consistent. Pooling of these data found that the proportion of individuals with an ICD who experience at least one shock during driving (appropriate or inappropriate) was in the order of 6.3%. A series of sensitivity analyses found the findings of this analysis to be robust.

Key Question 5: What is the risk of sudden death or incapacitation in individuals with low LVEF (<50%, <40%, <35%)?

1. **Decreasing LVEF increases the risk of sudden death or incapacitation among individuals with CVD (Strength of Evidence: Moderate).**

    - **Due to the fact that no more than two studies used the same levels of LVEF stratification, no attempt was made to determine a quantitative estimate of the risk of sudden death or incapacitation in individuals with low LVEF.**

    Ten low-to-moderate quality studies assessed the risk of sudden death or incapacitation in individuals with low LVEF. Five of these studies used multiple levels of LVEF stratification. The remaining five studies used a single level of LVEF stratification. These 10 studies consistently demonstrated that decreasing LVEF increases the risk of sudden death or incapacitation in individuals with CVD. However, several studies have indicated that although LVEF is an important risk factor for sudden death or incapacitation, it is not the only risk factor. In order to better predict sudden death or incapacitation, one should consider other risk factors along with LVEF. For example, one study noted that rather than using

particular risk markers, the use of a number of accumulated risk markers was a more powerful predictor for sudden death in patients with chronic heart failure.

Key Question 6: Is the relationship between LVEF and sudden death or incapacitation (if established) dependent on the underlying etiology of heart failure?

Due to a paucity of data, no conclusion pertaining to whether the relationship between sudden death or incapacitation and LVEF is drawn.

No studies met the inclusion criteria for this key question.

Preface

Organization of Report

This evidence report contains four major sections: 1) *Background;* 2) *Methods;* 3) *Synthesis of Results;* and 4) *Conclusions*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about CVD and driving. Also included in the *Background* section is information pertaining to current regulatory guidelines from FMCSA and three other government transportation safety agencies; the Federal Aviation Administration, the Federal Railroad Administration, and the Maritime Administration. In addition, we summarize equivalent information from three other countries that are generally considered to have well-developed medical fitness programs: Australia, Canada, and the United Kingdom. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature-searching, criteria for including studies in our analyses, an evaluation of study quality, an assessment of the strength of the evidence base for each question, and methods for abstracting and synthesis of clinical study results. The *Synthesis of Results* section of this report is organized by key question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when the data permit, both qualitatively and quantitatively (using meta-analysis). Each section in the *Synthesis of Results* section closes with our conclusions that are based on our assessment of the available evidence. This evidence report ends with a *Conclusions* section that briefly summarizes the answers to each of the questions addressed.

Scope

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12% of all occupation-related deaths) in the United States. About two-thirds of fatally injured truck workers were involved in highway crashes. According to the United States Department of Transportation, there were 137,144 nonfatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities.

The purpose of this evidence report is to address several key questions posed by FMCSA. Each of these key questions was carefully formulated by FMCSA so that the questions' answers will provide information necessary for the process of updating FMCSA's current medical examination guidelines titled, "Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Drivers."(1) The key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with CVD at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What are the risk factors for rupture of an aortic (abdominal or thoracic) aneurysm?

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Key Question 5: What is the risk for sudden death or incapacitation in individuals with low LVEF (<50%, <40%, <35%)?

Key Question 6: Is the relationship between LVEF and sudden death or incapacitation (if established) dependent on the underlying etiology of heart failure?

Background

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12% of all occupation-related deaths) in the United States (http://www.bls.gov/iif/oshcfoiarchive.htm#2004charts). About two-thirds of workers killed in the trucking industry are the consequence of highway crashes. According to the United States Department of Transportation, there were 137,144 nonfatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2005).

CVD may culminate in unpredictable and sudden incapacitation (e.g., heart attack), thus contributing to the potential for crash, injury, and death. The purpose of this evidence report is to assess and summarize the available data that address several key questions pertaining to CVD and the risk for a CMV crash.

CVD

CVD encompasses a broad category of disorders that affect the heart and/or blood vessels, including the following:

- Aneurysm
- Angina
- Arteriosclerosis and atherosclerosis
- Cardiac arrhythmia
- Cardiomyopathy
- Congenital heart disease
- CAD
- Heart failure (HF)
- Hypertension
- Myocardial infarction (MI)
- Pericardial disease
- Peripheral arterial disease with intermittent claudication
- Valvular heart disease
- Vasculitis
- Venous incompetence
- Venous thrombosis

CVDs that May Cause Sudden Debilitation

Sudden and unpredictable debilitation can adversely affect a driver's ability to operate a motor vehicle. This report focuses on several types of CVD that are known to cause sudden debilitation:

- Ischemic heart disease (including acute MI)
- Cardiac arrhythmia
- AAA and TAA
- Vasovagal syncope

In this section, we provide a general overview of these conditions. The conditions are then reviewed in greater detail in the relevant report subsections.

Ischemic Heart Disease

Ischemic heart disease develops when one or more coronary artery/arteries becomes narrowed or completely blocked. Lipids (arteriosclerosis) and blood clots (thrombosis) frequently cause these blockages, thus diminishing the passage of blood and vital oxygen through the affected vessels to the heart and producing ischemia. Ischemia can produce symptoms such as shortness of breath, fatigue, heart palpitations, dizziness, and chest discomfort or angina (pain). Angina is an important symptom of ischemic heart disease, because it often prompts the individual to seek medical attention. It can be categorized as stable (predictable, usually occurring with physical exertion) or unstable (unexpected and unpredictable, with pain that may be more severe) with the signs and symptoms. This is especially true of unstable angina, possibly heralding impending MI.[2] Other individuals may live with the symptoms of angina for years in a condition described as chronic ischemic heart disease, which may feature additional symptoms such as leg swelling and weight gain.(18)

Aneurysms

An aneurysm is a localized or diffused dilation of an artery to an internal volume of at least 50% greater than normal. AAAs are the most common, followed by aneurysms in the thoracic region and aneurysms of the thoracic and abdominal regions

[2] The sudden, dramatic cutoff of oxygen to the heart. Also known as a 'heart attack', a myocardial infarction (MI) can cause sudden and unpredictable incapacitation of the individual, potentially resulting in death.

(thoracoabdominal aneurysm). Such aneurysms can rupture, leading to hemorrhaging possibly associated with sudden incapacitation and potentially death.

Thrombosis

Thrombosis is defined as the formation or presence of a clot in a vein or an artery. Arterial thrombosis can cause MIs and strokes. Deep vein thrombosis (DVT) of the leg can dislodge, travel to the lungs, and cause a pulmonary embolism. MI, strokes, and pulmonary embolisms can all cause incapacitating and life-threatening conditions.

Cardiac Arrhythmias

Cardiac arrhythmia is any change in heartbeat rhythm from the normal sequence of electrical impulses in the heart.(19) Irregularities of heartbeat may occur in terms of how frequently the heart beats (a normal heartbeat is 60 to 100 beats per minute) or how regularly a heart beats (normal heartbeats are regular and predictable). Cardiac arrhythmias vary in degree of severity. The following list summarizes types of arrhythmias:

- Fibrillation: Fibrillation can originate from the atria or the ventricles. Atrial fibrillation is characterized by disorganized arterial systole, which causes a rapid, irregular heartbeat.(20) Ventricular fibrillation is usually due to CAD, and it is typified by extremely irregular heartbeat and may cause death within minutes.(18) Long QT syndrome (prolonged QT interval on electrocardiogram (ECG)) is associated with the development of ventricular tachyarrhythmia.(21)
- Ventricular tachycardia (VT): Rapid heartbeat (at least 120 beats per minute, and wide QRS intervals on ECG.(22)
- Atrial flutter: Rapid (250 to 400 beats per minute) but regular heartbeat.(23)
- Bradycardia: Slow heartbeat (60 beats per minute or less).(24)

Vasovagal Syncope

Individuals with vasovagal (neurocardiogenic) syncope experience sudden drops in blood pressure, which decreases blood flow and oxygen supply to the brain and may result in syncope (fainting). Although the condition itself is nonfatal, fainting at inappropriate times may precipitate accidents (e.g., falls, motor vehicle crashes) with potentially dire consequences.

Risk Factors for CVD

Risk factors for specific CVDs associated with sudden incapacitation are reported on in detail in the subsections of this report; this section provides a general overview of the risk factors for CVD.

Risk factors are of key importance for predicting major coronary heart disease (CHD), because approximately 90% of patients with CHD have at least one risk factor.(25) Most major risk factors for CVD are well known. They include: overweight/obesity, high total cholesterol (particularly with low levels of high-density lipoproteins (HDLs) and high levels of low-density lipoproteins (LDLs)), cigarette smoking, diabetes, and hypertension. Hypertension (blood pressure elevated above 140 mmHg systolic pressure or 90 mmHg diastolic) is a major risk factor for the development of CVD. Individuals with systolic pressure levels of 160 to 179 mmHg and/or diastolic blood pressure of 100 to 109 must be reassessed by a qualified physician biannually to continue driving commercially. Those with a minimum systolic blood pressure of 180 mmHg and/or diastolic blood pressure of 110 mmHg are prohibited from driving due to associated impaired judgment and compromised driving ability. When found in conjunction with organ damage, hypertension at this level is associated with a heightened risk of sudden incapacitation due to a coronary event, aortic aneurysm, or cerebrovascular crash.(26)

Much of the knowledge base regarding cardiovascular risk factors comes from epidemiologic studies. Three examples of such studies, with key risk factors identified, are summarized in Table 3 below.

Table 3. Studies on Risk Factors for the Development of CVD Identified by Cohort Studies

Name of Study	Population Studied	Risk Factors Identified	Citations
Framingham Heart Study	Caucasians in Small-Town New England	General CVD: High HDLs, low LDLs, overweight and obesity, left ventricular hypertrophy, greater age, cigarette smoking, and hypertension	(27-34)
The Cardiovascular Health Study	Adults aged at least 65 years	General CVD: advanced age, weight at age 50, and weight change after age 50 For MI: Systolic blood pressure, fasting glucose level, and hypertension For AAA: older age; male sex; history of angina, coronary heart disease, and myocardial infarction; lower ankle-arm blood pressure ratio; higher maximum carotid stenosis; greater intima-media thickness of the internal carotid artery; higher creatinine; lower HDL levels and higher LDL levels; and cigarette smoking	(35-38)
The Puerto Rico Heart Study	Hispanic-Americans	General CVD: alcohol consumption, serum lipid levels, hypertension, physical inactivity, smoking, blood glucose levels, obesity, and hematocrit	(39)

AAA Abdominal aortic aneurysm.
CVD Cardiovascular disease.
HDL High-density lipoprotein.
LDL Low-density lipoprotein.
MI Myocardial infarction.

Prevalence and Incidence of CVD

CVD has been the most common cause of death among Americans every year since 1900, with the single exception being the flu pandemic in the year of 1918. Cancer, chronic lower respiratory diseases, crashes, and diabetes mellitus[3] combined kill fewer Americans per year than CVD alone, with 2,440,000 (1 in 2.7) deaths attributed to CVD in 2003. CVD was cited as a contributing cause in an additional 1,408,000 deaths for a total of approximately 58% of all deaths in the United States.(25)

Data from the National Health and Nutrition Examination Survey estimated that 71,300,000 Americans had at least one form of CVD, with 43,900,000 of those individuals aged under 65 years (2003). Reported prevalence of CVD in American adults varies by race: 11.4% of Caucasians, 9.9% of African-Americans, 7.7% of Hispanics and Latinos, 5.6% of Asians, 16.5% of Native Hawaiians or other Pacific Islanders, and 13.8% of American Indians or Alaska Natives currently have some form of heart disease.

Data on prevalence and incidence of CVD are summarized in Table 4. Greater detail about the prevalence of specific CVDs of interest in this report is provided in the background section for each key question.

Table 4. Prevalence of CVDs and Incidence of New Events in the United States(25)

Disease	Number of People Affected	Proportion of Individuals with CVD (%)
Prevalence of Common CVDs		
Total CVDs	71,300,000	NA
Coronary Heart Disease	13,200,000	18.5%
Myocardial Infarction	7,200,000	10.0
Angina Pectoris	6,500,000	9.1
Heart Failure	5,000,000	7.0
Atrial Fibrillation	2,200,000*	2.8
Unstable Angina	2,000,000	2.8
Incidence of New Cardiovascular Events		
First-Time Coronary Attack	700,000 cases/year	NA
Repeat Coronary Attack	500,000 cases/year	NA

CVD Cardiovascular disease.
* http://www.americanheart.org/presenter.jhtml?identifier=4451
http://www.nhlbi.nih.gov/about/factbook/chapter4.htm#4_5

[3] CVD, cancer, chronic lower respiratory diseases, crashes, and diabetes mellitus are currently the top five causes of mortality in the United States.

Treatments for CVD

Treatments for CVD include stabilizing patients in acute crises and mitigating the long-term effects, and preventing new acute events in patients with chronic CVD. Pharmacotherapy and surgical management (which may include the implantation of a device) are mainstays of treatment for individuals with CVD, and these treatments are often administered in combination.

This section provides a general overview of treatment for CVD. Specific treatment information for the conditions addressed in this report is provided in the report subsections for each key question.

Pharmacotherapy

Currently there exist a wide variety of treatment options in pharmacotherapeutic management available to assist in the control of the course of CVD and associated pain. The information contained in Table 5 provides a general overview of these pharmacotherapies.

Table 5. Overview of Pharmacotherapy for CVD

Disease	Subtype	Pharmacotherapy	Citation
Angina	Stable, chronic	Initial choices include aspirin (or Clopidogrel when aspirin is absolutely contraindicated), beta-blockers (in patients with prior MI, or long-acting nondihydropyridine calcium antagonists instead) , ACE inhibitors (in patients with diabetes and/or left ventricular systolic dysfunction), LDL-lowering drugs (in patients with high cholesterol), nitroglycerin (for immediate angina relief), beta-blockers (when calcium antagonists are contraindicated)	(40)
	Unstable, acute	Nitroglycerine for pain as needed (with patients instructed to seek emergency medical attention if 3 doses at 5 minute intervals fail to relieve pain), beta-blockers for patients with ongoing pain (for patients with contraindications, a nondihydropyridine calcium antagonist (e.g., verapamil or diltiazem)), in the absence of severe left ventricular [LV] dysfunction or other contraindications), ACE inhibitors (when hypertension persists despite treatment with nitroglycerine and a beta-blocker in patients with LV systolic dysfunction or congestive heart failure (CHF), and in ACS patients with diabetes.	(41)
	Unstable, chronic	Beta- adrenergic blocking agents, calcium channel blocking agents, and nitrates.	(42)
	Unstable, chronic, low-risk for impending event	Aspirin, sublingual nitroglycerine.	(42)
Atrial Fibrillation	Acute	Intravenous beta-blockers or calcium channel antagonists (e.g., verapamil, diltiazem) with special caution in patients with hypotension or heart failure.	(43)
	Chronic (including arterial flutter)	Digoxin (possibly with a beta-blocker or calcium channel antagonist), antithrombotics (such as aspirin).	(43)
Myocardial Infarction	Acute	Non-coated aspirin, beta-blockers (e.g., metoprolol), intravenous unfractionated heparin, nitroglycerine, ACE inhibitors, analgesics.	(42)
Tachycardia	Acute episodes or chronic care	Recommended pharmacotherapy depends on individual patients' ECG findings, but may include at least one of the following: adenosine, verapamil, diltiazem, beta blockers, amiodarone, digoxin, flecainide, butilide, procainamide, sotalol, lidocaine, adenosine.	(44)

ACE Angiotensin-converting enzyme.
ACS Acyte coronary syndrome.
CHF Congestive heart failure.
LDL Low-density lipoprotein.
LV Left ventricular.
MI Myocardial infarction.

Interventional Treatments for CVD

Catheter-based interventions and surgical procedures are used in conjunction with pharmacologic therapy to treat a variety of cardiovascular diseases. The following examples summarize some common cardiovascular disorders and their treatments:

- CAD: Cardiac catheterization with balloon angioplasty and stenting, so-called "percutaneous intervention" (PCI), and coronary artery bypass grafting (CABG).
- Valvular heart disease: Insufficiency (leaking valves) treated with drugs and/or surgical repair or replacement. Stenotic (narrowed valves) treated with surgical replacement or, less commonly, balloon angioplasty.
- Bradycardia: Pacemaker
- Tachycardia:
    - Ablation using catheter in catheterization laboratory.

  - ICD to protect against sudden cardiac death in patients with either risk for sudden cardiac arrest or those who have survived a life-threatening ventricular arrhythmia.
  - Surgical resection (aneurysm with VT—especially in setting of CAD).
- Arterial aneurysms:
  - Thoracic and abdominal aneurysms treated with intravascular stents deployed in catheter-based procedure, or resected in operating room.
  - Peripheral aneurysms usually treated with surgical resection.

Commercial Drivers and CVD

The prevalence of CVD is believed to be higher among commercial drivers than in the general population, with some speculation as to the interaction of behavioral (lifestyle) and occupational factors on the development of CVD. Lifestyle factors that may contribute to the development of CVD among commercial drivers include the following:

- Unhealthy eating habits(45)
- Smoking(45-47)
- Alcohol use(45)
- Physical inactivity(45)
- Overweight/obese body mass index(46)

Occupational factors associated with the development of CVD in commercial drivers include the following:

- Long working hours(45,48)
- Irregular working hours(45)
- Sedentary nature of the job(48)
- Exposure to chemical agents(45), including automobile exhaust fumes(48)
- Exposure to excessive noise(48) (in urban environments)

The type of commercial driving that an individual performs may also affect risk for CVD. For instance, studies have found that:

- long-distance truck drivers are more likely to suffer from ischemic heart disease (including MI) than short-distance drivers(49);

- Bus drivers on urban routes are more likely to suffer MI than taxi and bus drivers.(50); and
- Bus drivers are more likely to suffer from ischemic heart disease than truck drivers.(51)

Current Medical Fitness Standards and Guidelines

Current Medical Fitness Standards and Guidelines for CMV Drivers in the United States

Current Medical Fitness Standards

The current medical qualification standard for fitness to drive a CMV (49 CFR 391.41(b) subparts 4 and 6) states the following (see: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.asp?section=391.41):

A person is physically qualified to drive a CMV if that person

- has no current clinical diagnosis of MI, angina pectoris, coronary insufficiency, thrombosis, or any other CVD of a variety known to be accompanied by syncope, dyspnea, collapse, or congestive cardiac failure; and
- has no current clinical diagnosis of high blood pressure likely to interfere with his/her ability to operate a CMV safely.

Current Medical Guidelines

In 2002, FMCSA published a series of medical guidelines developed by a cardiovascular advisory panel.(26) Unlike standards that are regulations that a medical examiner must follow, these guidelines are recommendations that the medical examiner should follow. While not law, the guidelines are intended as standards of practice for medical examiners.

Ischemic Heart Disease

Current FMCSA CVD Advisory Panel guidelines pertaining to ischemic heart disease are summarized in Table 6.

Table 6. FMCSA CVD Advisory Panel Guidelines Pertaining to Ischemic Heart Disease

Diagnosis	Physiologic/Functional	Certification	Recertification
Asymptomatic, healthy	Low CHD event risk. Assess for clinically apparent risk factors. Use, when possible, Framingham risk score model to predict 10-year CHD event risk; increasing age is a surrogate marker for increasing atherosclerotic plaque burden.	Yes, if asymptomatic. Rarely disqualifying alone.	Biennial
Asymptomatic, high-risk person (as designated by CHD risk-equivalent condition)* Asymptomatic, high-risk person >45 years with multiple risk factors for CHD	Subclinical coronary atherosclerosis is a concern; High-risk status requires close physician follow-up and aggressive comprehensive risk factor management.	Yes, if asymptomatic. No if: • Abnormal ETT** • Ischemic changes on ECG † • Functional incapacitation by one of conditions.	Annual
Post MI	Risk of recurrent major cardiac event highest within the first months post-MI; Drivers in a rehabilitation program can receive comprehensive secondary prevention therapy.	No if: Recurrent angina symptoms; • Post-MI ejection fraction <40% (by ECG or ventriculogram); • Abnormal ETT demonstrated prior to planned work return; • Ischemic changes on rest ECG; • Poor tolerance to current cardiovascular medications.	
		Yes if: • At least 2 months post-MI; • Cleared by cardiologist; • No angina; • Post-MI ejection fraction >40% (by ECG or ventriculogram); • Tolerance to current cardiovascular medications.	Annual Biennial ETT at minimum (If test positive or inconclusive, imaging stress test may be indicated); Cardiologist examination recommended.
Angina Pectoris	Lower end of spectrum among CHD patients for risk of adverse clinical outcomes. Condition usually implies at least one coronary artery has hemodynamically significant narrowing.	Yes, if asymptomatic.	Annual Biennial ETT at minimum (If test positive or inconclusive, imaging stress test may be indicated); Cardiologist examination recommended.
		No if: • Rest angina or change in angina pattern within 3 months of examination; • Abnormal ETT; • Ischemic changes on rest ECG; • Intolerance to cardiovascular therapy.	
Post PCI	Rapid recovery for elective PCIs for stable angina; delayed restenosis is the major PCI limitation and requires intensive secondary prevention.	Yes if: • At least 1 week after procedure; • Cardiologist's approval; • Tolerance to medications. • ETT 3 to 6 months after PCI.	Annual Recommend Cardiologist examination. Biennial ETT at minimum (If test positive or inconclusive, imaging stress test may be indicated).

Diagnosis	Physiologic/Functional	Certification	Recertification
		No if: • Incomplete healing or complication at vascular access site; • Rest angina; • Ischemic ECG changes.	
Post Coronary Artery Bypass Surgery (CABG)	Delay in return to work to allow sternal incision healing. Because of increasing risk of graft closure over time, ETT is obtained.	Yes if: • At least 3 months after CABG; • LVEF >40% post CABG; • Approval by cardiologist; • Asymptomatic; and tolerance to medications.	Annual After 5 years: Annual ETT. Imaging stress test may be indicated.

CABG Coronary artery bypass grafting.
CHD Coronary heart disease.
ECG Electrocardiogram.
ETT Exercise treadmill time.
LVEF Left ventricular ejection fraction.
MI Myocardial infarction.
PCI Percutaneous coronary intervention.

Hypertension

Current FMCSA CVD Advisory Panel guidelines pertaining to hypertension are summarized in Table 7.

Table 7. FMCSA CVD Advisory Panel Guidelines Pertaining to Hypertension

Diagnosis	Physiologic/Functional	Certification	Recertification
Essential Hypertension	Evaluate for other clinical CVD including TOD. Presence of TOD, CVD, or diabetes may affect therapy selected.		
Stage 1 (140-159/90-99 mm Hg)	Usually asymptomatic; Low risk for near-term incapacitating event.	Yes Rarely disqualifying alone.	Annual BP ≤140/90 at annual exam; If not, but <160/100, certification extended 1 time for 3 months.
Stage 2 (160-179/100-109 mm Hg)	Low risk for incapacitating event; risk increased in presence of TOD; Indication for pharmacologic therapy.	Yes, one time certification for 3 months.	
		Yes, at recheck if: BP ≤140/90mmHg Certify for 1 year from date of initial exam.	Annual BP ≤140/90.
Stage 3 (>180/110 mm Hg)	High risk for acute hypertension-related event.	No, immediately disqualifying	
		Yes, at recheck if: • BP ≤140/90 mm/Hg. and treatment is well tolerated. • Certify for 6 months from date of initial exam.	Every 6 months; BP ≤140/90.
Secondary Hypertension	Evaluation warranted if persistently hypertensive on maximal or near-maximal doses of 2-3 pharmacologic agents; May be amenable to surgical/specific therapy.	Based on above stages. Yes if: • Stage 1 or nonhypertensive. • At least 3 months after surgical correction.	Annual BP ≤140/90

BP Blood pressure.
CVD Cardiovascular disease.

TOD Target organ damage.

Valvular Heart Disease and Myocardial Disease

Current FMCSA CVD Advisory Panel guidelines pertaining to valvular heart disease and myocardial disease are summarized in Table 8.

Table 8. FMCSA CVD Advisory Panel Guidelines Pertaining to Valvular Heart Disease and Myocardial Disease

Diagnosis	Physiology/ Functional Status	Certification	Recertification
Mitral Stenosis			
Mild Mitral Stenosis MVA ≥1.6 cm^2	In the presence of symptoms consistent with moderate to severe mitral stenosis but a calculated valve area suggesting mild mitral stenosis, the severity of the stenosis should be reassessed and an alternative explanation for symptoms should be considered.	Yes, if asymptomatic.	Annual
Moderate Mitral Stenosis MVA 1.0 to 1.6 cm^2		Yes, if asymptomatic.	Annual
Severe Mitral Stenosis MVA ≤1.0 cm^2		No if: • NYHA Class II or higher; • Atrial fibrillation; • Pulmonary artery pressure ≥50% of systemic pressure; • Inability to exercise for >6 METs on Bruce protocol (Stage II).	
		Yes if: • At least 4 weeks post percutaneous balloon mitral valvotomy; or • At least 3 months post surgical commissurotomy; • Clearance by cardiologist.	Annual Annual evaluation by a cardiologist.
Mitral Regurgitation			
Mild Mitral Regurgitation		Yes if: • Asymptomatic; • Normal LV size and function; • Normal PAP.	Annual Annual echo not necessary.
Moderate Mitral Regurgitation		Yes if: • Asymptomatic; • Normal LV size and function; Normal PAP.	Annual Annual Echocardiogram.
Severe Mitral Regurgitation		Yes, if asymptomatic.	Annual Echocardiogram every 6-12 months. Exercise testing may be helpful to assess symptoms.
		Yes if: • At least 3 months postsurgery. • Asymptomatic; cleared by cardiologist.	Annual

Diagnosis	Physiology/ Functional Status	Certification	Recertification
		No if: • Symptomatic; • Inability to achieve >6 METs on Bruce protocol; • Ruptured chordae or flail leaflet; • Atrial fibrillation; • LV dysfunction;* • Thromboembolism; • Pulmonary artery pressure 50% of systolic arterial pressure.	
Aortic Stenosis			
Mild Aortic Stenosis (AVA ≥1.5 cm^2)	If symptoms are consistent with aortic stenosis but calculated valve area suggests mild aortic stenosis, the severity of the stenosis and an alternative explanation for symptoms needs to be reassessed.	Yes, if asymptomatic.	Annual Echocardiogram every 5 years.
Moderate Aortic Stenosis (AVA ≥1.0-1.5 cm^2)		Yes, if asymptomatic.	Annual Echocardiogram every 1 to 2 years.
		Yes if at least 3 months after surgery.	Annual
		No if: • Angina, Heart failure, Syncope; • Atrial fibrillation; • LV dysfunction with EF <50%; • Thromboembolism.	
Severe Aortic Stenosis (AVA <1.0 cm^2)		No, irrespective of symptoms or LV function.	
		Yes, if at least 3 months after surgery.	Annual
Aortic Regurgitation			
Mild Aortic Regurgitation		Yes, if asymptomatic.	Annual Echocardiogram every 2 to 3 years.
Moderate Aortic Regurgitation		Yes if: • Normal LV function; • No or mild LV enlargement.	Annual Echocardiogram every 2 to 3 years.
Severe Aortic Regurgitation		Yes if: • Asymptomatic; • Normal LV function (EF ≥50%); • LV dilatation (LVEDD <60 mm; LVESD <50 mm).	Every 6 months. Echocardiogram every 6 to 12 months.
		If LVEDD ≥60 mm or LVESD ≥50 mm.	Every 4 - 6 months. Echocardiogram every 4 - 6 months if no surgery performed.
		No if: • Symptoms; • Unable to complete Bruce protocol Stage II; • Reduced EF <50%; • LV dilatation; • LVEDD >70 mm; or LVESD >55 mm.	

Diagnosis	Physiology/ Functional Status	Certification	Recertification
		Yes if: • Valve surgery and at least 3 months postsurgery. • Asymptomatic; cleared by cardiologist.	Annual
Mild Aortic Regurgitation		Yes, if asymptomatic.	Annual Echocardiogram every 2 to 3 years.
Moderate Aortic Regurgitation		Yes if: • Normal LV function; • No or mild LV enlargement.	Annual Echocardiogram every 2 to 3 years.
Valve replacement			
Mechanical Valves		Yes if: • At least 3 months post-op; • Asymptomatic; Cleared by cardiologist.	Annual Recommend evaluation by cardiologist.*
		No if: • Symptomatic; LV dysfunction-EF <40%; • Thromboembolic complication post procedure; • Pulmonary hypertension; • Unable to maintain adequate anticoagulation (based on monthly INR checks).	
	Prosthetic valve dysfunction.	No	
		Yes if: • Surgically corrected; • At least 3 months post-op; • Asymptomatic; • Cleared by cardiologist.	Annual Recommend evaluation by cardiologist
	Atrial fibrillation.	Yes if: • Anticoagulated adequately for at least 1 month and monitored by at least monthly INR; • Rate/rhythm control adequate; • Cleared by cardiologist.	Annual
Biologic Prostheses	Anticoagulant therapy not necessary in patients in sinus rhythm (after initial 3 months), in absence of prior emboli or hypercoagulable state.	Yes if: • At least 3 months post-op; Asymptomatic; • None of above disqualifying criteria for mechanical valves; • Cleared by cardiologist.	Annual Recommend evaluation by cardiologist.*
Cardiomyopathies and Congestive Heart Failure			
Hypertrophic Cardiomyopathy		No	
Idiopathic Dilated Cardiomyopathy and Congestive Heart Failure		No, if symptomatic CHF.	
		No if: • Asymptomatic; • Ventricular arrhythmias present; and • LVEF ≤50%.	

Diagnosis	Physiology/ Functional Status	Certification	Recertification
		No if: • Asymptomatic; • No ventricular arrhythmias but LVEF <40%.	
		Yes if: • Asymptomatic; • No ventricular arrhythmias; • LVEF 40% to 50%.	Annual Requires annual cardiology evaluation including Echocardiography and Holter monitoring.
Restrictive Cardiomyopathy		No	

AVA Aortic valve area.
CHF Congestive heart failure.
EF Endothelial function.
INR International normalized ratio.
LV Left ventricle.
LVEDD Left ventricular end diastolic diameter.
LVEF Left ventricular ejection fraction.
LVESD Left ventricular end systolic diameter.
METs Metabolic equivalents.
MVA Mitral valve area.
NYHA New York heart association.
PAP Pulmonary artery pressure.

Cardiac Arrhythmias, Pacemakers, Implantable Defibrillators

Current FMCSA CVD Advisory Panel guidelines pertaining to cardiac arrhythmias, pacemakers, and implantable defibrillators are summarized in Table 9.

Table 9. FMCSA CVD Advisory Panel Guidelines Pertaining to Cardiac Arrhythmias, Pacemakers, and Implantable Defibrillators

Diagnosis	Physiology/ Functional	Recertification	Re-certification
Supraventricular Tachycardias			
Lone Atrial Fibrillation	Good prognosis and low risk for stroke.	Yes	Annual
Atrial Fibrillation as cause of or a risk for stroke	Risk for stroke decreased by anticoagulation.	Yes if: • Anticoagulated adequately for at least 1 month; • Anticoagulation monitored by at least monthly INR; • Rate/rhythm control deemed adequate (Recommend assessment by cardiologist).	Annual
Atrial Fibrillation following thoracic surgery	Good prognosis and duration usually limited.	In atrial fibrillation at time of return to work; • Yes if: • Anticoagulated adequately for at least 1 month; • Anticoagulation monitored by at least monthly INR; • Rate/rhythm control deemed adequate (Recommend assessment by cardiologist).	Annual

Diagnosis	Physiology/ Functional	Recertification	Re-certification
Atrial Flutter	Same as for atrial fibrillation.	Same as for atrial fibrillation. Yes if: • Isthmus ablation performed at least 1 month after procedure; • Arrhythmia successfully treated; • Cleared by electrophysiologist.	Same as for atrial fibrillation. Annual
Multifocal Atrial Tachycardia	Often associated with comorbidities, such as lung disease, that may impair prognosis.	Yes if asymptomatic (unless associated condition is disqualifying)	Annual
		No, if symptomatic.	
		Yes if symptoms controlled and secondary cause is not exclusionary.	Annual.
Atrioventricular Nodal Reentrant Tachycardia (AVNRT) Atrioventricular Reentrant Tachycardia (AVRT) and Wolff-Parkinson-White (WPW) Syndrome Atrial Tachycardia Junctional Tachycardia	Prognosis generally excellent, but may rarely have syncope or symptoms of cerebral hypoperfusion. For those with WPW, preexcitation presents risk for death or syncope if atrial fibrillation develops.	No if symptomatic; or WPW with atrial fibrillation.	
		Yes if: • Asymptomatic; • Treated and asymptomatic for at least 1 month and assessed and cleared by expert in cardiac arrhythmias.	Annual Recommend consultation with cardiologist.
Ventricular Arrhythmias			
Coronary Heart Disease (CHD)	Sustained VT: Poor prognosis and high risk.	No	
	NSVT, LVEF <0.40: Unfavorable prognosis.	No	
	NSVT, LVEF ≥0.40: Generally considered to have good prognosis.	No, if symptomatic.	
		Yes if: • Asymptomatic. • At least 1 month after drug or other therapy is successful; • Cleared by cardiologist.	Annual cardiology examination required.
Dilated Cardiomyopathy	NSVT (LVEF ≤0.40).	No	
	Sustained VT, any LVEF.	No	
	Syncope/near syncope, any LVEF: High risk.	No	
Hypertrophic Cardiomyopathy	Variable but uncertain prognosis.	No	
Right Ventricular Outflow VT	Favorable prognosis and low risk for syncope.	No, if symptomatic.	
		Yes, if asymptomatic.	Annual Recommend evaluation by cardiologist.
		Yes if: • At least 1 month after drug or other therapy successful; • Asymptomatic; • Cleared by electrophysiologist.	Annual Evaluation by cardiologist required.
Idiopathic Left Ventricular VT	Favorable prognosis and low risk for syncope.	No, if symptomatic.	
		Yes, if asymptomatic.	Annual Recommend evaluation by cardiologist.

Diagnosis	Physiology/ Functional	Recertification	Re-certification
		Yes if: • At least 1 month after successful drug therapy or ablation; • Cleared by electrophysiologist.	Annual Evaluation by cardiologist required.
Long QT Interval Syndrome	High risk for ventricular arrhythmic death.	No	
Brugada Syndrome	High risk for ventricular arrhythmic death.	No	
Bundle Branch Blocks and Hemiblocks			
Bundle Branch Block Axis Deviation	Progression of disease in the conduction system can lead to third-degree heart block with total loss of electrical connection between the atria and ventricles, causing syncope or sudden death.	Yes if asymptomatic (depends on risk from underlying heart disease).	Every 2 years.
		Yes, if • Treated for symptomatic disease (see pacemaker); • No disqualifying heart disease; • Cleared by cardiologist.	Annual
		No, if symptomatic.	
Pacemakers			
Sinus Node Dysfunction	Variable long term prognosis depending on underlying disease, but cerebral hypoperfusion corrected by support of heart rate by pacemaker.	No	
		Yes if: • 1 month after pacemaker implantation; documented correct function by pacemaker center; • Underlying disease is not disqualifying.	Annual Documented pacemaker checks.
Atrioventricular (AV) Block	Variable long term prognosis depending on underlying disease, but cerebral hypoperfusion corrected by support of heart rate by pacemaker.	No	
		Yes if: • 1 month after pacemaker implantation and documented correct function by pacemaker center • Underlying disease is not disqualifying.	Annual Documented pacemaker checks.
Neurocardiogenic Syncope	Excellent long-term survival prognosis but there is risk for syncope that may be due to cardioinhibitory (slowing heart rate) or vasodepressor (drop in blood pressure) components, or both. Pacemaker will affect only cardioinhibitory component, but will lessen effect of vasodepressor component.	No, with symptoms.	
		Yes if: • 3 months* after pacemaker implantation; • Documented correct function by pacemaker center; • Absence of symptom recurrence.	Annual Documented pacemaker checks; Absence of symptom recurrence.
Hypersensitive Carotid Sinus with	Excellent long-term survival	No, with symptoms.	

Diagnosis	Physiology/ Functional	Recertification	Re-certification
Syncope	prognosis but there is risk for syncope that may be due to cardioinhibitory (slowing heart rate) or vasodepressor (drop in blood pressure) components, or both. Pacemaker will affect only cardioinhibitory component, but will lessen effect of vasodepressor component.	Yes if: • 3 months* after pacemaker implantation; • Documented correct function by pacemaker center; • Absence of symptom recurrence.	Annual Documented regular pacemaker checks; and Absence of symptom recurrence.
Implantable Defibrillators			
Primary Prevention	Patient has high risk for death and sudden incapacitation.	No	
Secondary Prevention	Patient demonstrated to have high risk for death and sudden incapacitation.	No	

INR International normalized ratio.
LVEF Left ventricular ejection fraction.
NSVT Nonsustained ventricular tachycardia.
VT Ventricular tachycardia.

Congenital Heart Disease

Current FMCSA CVD Advisory Panel guidelines pertaining to congenital heart disease are summarized in Table 10.

Table 10. FMCSA CVD Advisory Panel Guidelines Pertaining to Congenital Heart Disease

Diagnosis	Physiology/Functional	Certification	Recertification
Aortic Congenital Heart Disease			
Bicuspid Aortic Valve	May result in aortic stenosis or regurgitation (see section on Valvular Diseases), aortic root enlargement, aortic aneurysm formation and aortic rupture.	See section on Valvular Diseases	See table pertaining to Valvular Diseases.
		No if aortic transverse diameter >5.5 cm	
		Yes if surgical intervention successfully performed	Annual
Subvalvular Aortic Stenosis	Mild = favorable Has potential for progression.	Yes if no valvular abnormality or hypertrophic cardiomyopathy.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease is required.
	Moderate or severe = unfavorable.	No if symptomatic and mean pressure gradient >30 mmHg.	
		Yes if at least 3 months after successful surgical resection when cleared by cardiologist knowledgeable in congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease required, including echocardiogram.
Discrete Supravalvular Aortic Stenosis	Unfavorable prognosis due to associated coronary and aortic disorder.	No, unless surgery.	
		Yes if: • At least 3 months postsurgical intervention; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease is recommended.
Marfan Syndrome	Cardiovascular disorders are the major cause of morbidity and mortality including	Yes if no cardiovascular involvement.	Annual Evaluation by cardiologist

Diagnosis	Physiology/Functional	Certification	Recertification
	risk of sudden death.	No if: • Any aortic root enlargement; • moderate or more severe aortic regurgitation; • mild mitral regurgitation related to mitral valve prolapse; • LV dysfunction with EF <40% and no associated valve disease.	knowledgeable in adult congenital heart disease required including aortic root imaging and echocardiography.
Atrial Septal Defects			
Atrial Septal Defect: Ostium Secundum	Small = favorable.	Yes if asymptomatic.	Annual Evaluation by cardiologist knowledgeable in congenital heart disease, including echocardiogram.
	Moderate to large = unfavorable.	No if: • Symptoms of dyspnea, palpitations or a paradoxic embolus; • pulmonary hypertension; • right-to-left shunt; • pulmonary to systemic flow ratio >1.5 to 1. 0	
		Yes if: • At least 3 months after surgery or at least 4 weeks after device closure; • asymptomatic; • clearance by cardiologist knowledgeable in adult congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease every two years.
Atrial Septal Defect: Ostium Primum	Small ASD = favorable prognosis.	Yes, if asymptomatic.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease required, including echocardiogram.
	Moderate to large ASD = unfavorable prognosis.	No if: • Symptoms of dyspnea, palpitations, or a paradoxic embolus; • Echo-Doppler demonstrates pulmonary artery pressure >50% systemic; • Echo-Doppler demonstrates right-to-left shunt; • pulmonary to systemic flow ratio greater than 1.5 to 1 heart block on an ECG; • more than mild mitral valve regurgitation; • left ventricular outflow tract obstruction with a gradient >30 mmHg.	

Diagnosis	Physiology/Functional	Certification	Recertification
		Yes if: • At least 3 months after surgical intervention if none of the above disqualifying criteria; • no symptomatic arrhythmia; • no significant residual shunt; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease.
Sinus Venosus Atrial Septal Defect	Usually associated with anomalous pulmonary venous connection. Prognosis depends on size of atrial septal defect. Commonly associated with sinus node dysfunction, particularly after surgery.	Yes if: Small shunt and hemodynamically insignificant.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease.
		No if: • Symptoms of dyspnea, palpitations, or a paradoxic embolus; • Echo-Doppler examination demonstrating pulmonary artery pressure greater than 50% systemic; • Echo-Doppler examination demonstrating a right-to-left shunt; • a pulmonary to systemic flow ratio greater than 1.5 to 1 • heart block or sinus node dysfunction on an ECG.	
		Yes if: • At least 3 months after surgical intervention; • hemodynamics are favorable; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease, including Holter monitor.
Ventricular Septal Defects			
Ventricular Septal Defect	Small = favorable.	Yes, if small shunt.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease recommended.
	Moderate to large VSD has effect on pulmonary pressure and ventricular size and function.	No if: • Moderate to large VSD; • symptoms of dyspnea, palpitations, or syncope; • pulmonary artery hypertension; • right-to-left shunt, left ventricular enlargement or reduced function; • pulmonary to systemic flow ratio greater than 1.5 to 1.0	

Diagnosis	Physiology/Functional	Certification	Recertification
		Yes if: • At least 3 months after surgery; • none of above disqualifying criteria; • no serious dysrhythmia on 24 hour Holter monitoring; • QRS interval <120 ms; • (If right ventricle conduction delay >120 ms on ECG, can be certified if invasive His bundle studies show no infra-His block or other serious electrophysiologic disorder); • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease, including 24 hour Holter Monitoring
Congenital Heart Disease			
Patent Ductus Arteriosus (PDA)	Small = favorable.	Yes, if small shunt.	Annual
	Moderate to large = unfavorable.	No if: • Symptoms of dyspnea or palpitations; • pulmonary hypertension; • right-to-left shunt; • progressive LV enlargement or decreased systolic function.	
		Yes if: • At least 3 months after surgery or 1 month after device closure; • none of above disqualifying criteria; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Should have evaluation by cardiologist knowledgeable in adult congenital heart disease.
Coarctation of the Aorta	Mild = favorable.	Yes if: • Mild and unoperated; • BP controlled; • no associated disqualifying disease.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease recommended.
	Moderate or severe = unfavorable prognosis.	No	
Coarctation of the Aorta After Intervention	Unfavorable prognosis with persistent risk of cardiovascular events.	Yes, if perfect repair.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease required.
Pulmonary Valve Stenosis (PS)	Mild and moderate = favorable.	Yes, if mild or moderate.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease.

Diagnosis	Physiology/Functional	Certification	Recertification
	Severe PS may be unfavorable, associated with arrhythmias, and rarely, sudden death.	No if • Symptoms of dyspnea, palpitations, or syncope; • pulmonary valve peak gradient >50 mmHg with normal output; • RV pressure >50% systemic pressure; • >mile RVH; • >mild RV dysfunction; • >moderate pulmonary valve regurgitation; • Main pulmonary artery >5 cm.	
		Yes if: • 3 months after surgical valvotomy or 1 month after balloon valvuloplasty; • none of above disqualifying criteria; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Recommend evaluation by cardiologist knowledgeable in adult congenital heart disease.
Other Causes of Right Ventricular Outflow Obstruction in People with Congenital Heart Disease.	Double-chambered right ventricle Infundibular pulmonary stenosis Supravalvar pulmonary stenosis Pulmonary artery stenosis.	Yes if hemodynamic data and criteria similar to individuals with isolated pulmonary valve stenosis who are eligible for certification.	Annual Recommend evaluation by cardiologist knowledgeable in adult congenital heart disease.
Ebstein Anomaly	Mild = favorable.	Yes if: • Mild; • asymptomatic; • no intracardiac lesions; • no shunt; • no symptomatic arrhythmia or accessory conduction; • only mild cardiac enlargement; • only mild RV dysfunction.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease.
	Moderate and severe variants = unfavorable.	No	
		Yes if: • At least 3 months postsurgical intervention; • None of above disqualifying features.	Annual Echocardiogram and evaluation by cardiologist knowledgeable in adult congenital heart disease required.
Tetralogy of Fallot	Unfavorable in the unrepaired state.	No, if uncorrected.	
Transposition of the Great Vessels	Unfavorable if not correctable.	No	
	Atrial switch repair (Mustard or Senning procedures). Unfavorable long-term prognosis.	No	
	After Rastelli repair.	Yes if asymptomatic and excellent result obtained from surgery.	Annual Evaluation by cardiologist knowledgeable in adult congenital heart disease.
	After arterial switch repair, prognosis appears favorable.	No – Data currently not sufficient to support qualification in this group.	

Diagnosis	Physiology/Functional	Certification	Recertification
Congenitally Corrected Transposition	95% have associated intracardiac lesions. Conduction system is inherently abnormal.	Yes if none of below disqualifying criteria met.	Annual Required annual evaluation by cardiologist knowledgeable in adult congenital heart disease, includes echocardiography and 24 hour Holter monitor.
		No if: • Symptoms of dyspnea, palpitations, syncope, or paradoxical embolus; • intracardiac lesion such as VSD; • >moderate pulmonary stenosis with a pulmonary ventricular pressure >50% systemic; • >mild RV or LV enlargement or dysfunction; • moderate or greater tricuspid valve (systemic atrioventricular valve) regurgitation; • history of atrial or ventricular arrhythmia; • ECG with heart block; • right-to-left shunt or significant residual left-to-right shunt.	
		Yes if: • At least 3 months after surgery; • none of above disqualifying criteria; • if prosthetic valve - must meet requirements for that valve; • cleared by cardiologist knowledgeable in adult congenital heart disease.	Annual Recommend evaluation by cardiologist knowledgeable in adult congenital heart disease.

ASD Atrial septal defect.
BP Blood pressure.
ECG Electrocardiogram.
EF Endothelial function.
LV Left ventricle.
RV Right ventricle.
RVH Right ventricular hypertrophy.
VSD Ventricular septal defect.

Aortic Aneurysms, Peripheral Vascular Disease, Venous Disease

Current FMCSA CVD Advisory Panel guidelines pertaining to aortic aneurysms, peripheral vascular disease, and venous disease are summarized in Table 11.

Table 11. FMCSA CVD Advisory Panel Guidelines Pertaining to Aortic Aneurysms, Peripheral Vascular Disease, and Venous Disease

Diagnosis	Physiology/ Functional	Certification	Recertification
Aortic Aneurysms			
Abdominal Aortic Aneurysm	Evaluate for associated CVDs		
	Aneurysm <4.0 cm	Yes, if asymptomatic.	Annual
	Aneurysm 4.0 to <5.0 cm	Yes if: • Asymptomatic; • cleared by vascular specialist.	Annual Ultrasound to identify change in size.

Diagnosis	Physiology/ Functional	Certification	Recertification
		No, if: • Symptomatic; • surgery recommended by vascular specialist.	
		Yes if at least 3 months after surgical repair cleared by cardiovascular specialist	Annual
	Aneurysm ≥5.0 cm	No.	
		Yes if at least 3 months after surgical repair cleared by cardiovascular specialist	Annual
Thoracic Aneurysm	Evaluate for associated CVDs.	No, if >3.5cm	
		Yes if at least 3 months after surgical repair cleared by cardiovascular specialist	Annual
Aneurysms of Other Vessels	Assess for risk of rupture and for associated ideovascular diseases.	No	
		Yes if at least 3 months after surgical repair cleared by cardiovascular specialist	Annual
Peripheral Vascular Disease			
Peripheral Vascular Disease	Evaluate for associated CVDs.	Yes, if no other disqualifying cardiovascular condition met.	Annual
Intermittent Claudication	Most common presenting manifestation of occlusive arterial disease.	Yes if: • At least 3 months after surgery; • relief of symptoms; • no other disqualifying CVD met.	Annual
	Rest pain.	No, if symptoms.	
		Yes if: • At least 3 months after surgery; • relief of symptoms and signs; • no other disqualifying CVD met.	Annual
Venous Disease			
Acute Deep Vein Thrombosis (DVT)		No, if symptoms.	
		Yes if: • No residual acute deep venous thrombosis; • If on Coumadin: Regulated for at least 1 month; • INR monitored at least monthly.	Annual
Superficial Phlebitis		Yes if: • DVT ruled out; • No other disqualifying CVD met.	Biennial
Pulmonary Embolus		No, if symptoms.	
		Yes if: • No pulmonary embolism for at least 3 months; • on appropriate long-term treatment; • If on Coumadin, regulated for at least 1 month INR monitored at least monthly; • No other disqualifying CVD met.	Annual

Diagnosis	Physiology/ Functional	Certification	Recertification
Chronic Thrombotic Venous Disease		Yes, if no symptoms.	Biennial
Varicose Veins		Yes, if no complications.	Biennial
Coumadin	Use of INR required.	Yes if: • Stabilized for 1 month; • INR monitored at least monthly.	Annual

CVD Cardiovascular disease.
DVT Deep-vein thrombosis.
INR International normalized ratio.

Heart Transplantation

Current FMCSA CVD Advisory Panel guidelines pertaining to heart transplantation are summarized in Table 12.

Table 12. FMCSA CVD Advisory Panel Guidelines Pertaining to Heart Transplantation

Diagnosis	Physiology/Functional	Certification	Recertification
Heart Transplantation	Special attention to: • accelerated atherosclerosis; • transplant rejection; • general health.	Yes if: • At least 1 year post-transplant; • asymptomatic; • stable on medications; • no rejection; • consent from cardiologist to drive commercially.	Biannual Clearance by cardiologist required.

Medical Fitness Standards and Guidelines for Individuals Performing Transportation Safety in the United States

Current medical fitness standards and guidelines for individuals performing transportation safety in the United States are summarized in Table 13. Included in the table are pertinent rules and guidance for pilots, railroad workers, and merchant mariners.

Table 13. Standards and Guidelines for CVDs from U.S. Government Transportation Safety Agencies

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
Angina Pectoris	No medical history or current clinical diagnosis of angina.	No specific standards or guidelines.	No specific standards or guidelines.
Coronary Heart Disease	Coronary heart disease that has required treatment or, if untreated, that has been symptomatic or clinically significant is disqualifying	No specific standards or guidelines.	Functional class II, III or IV NYHA – (New York Heart Association) may be disqualifying.
Exemptions, Additional tests, or Qualifying Information.	Applicants with cardiovascular conditions may be certified if the conditions listed under Disease Protocols are met.	Not applicable.	Physical examination listing medical conditions that include cardiovascular problems. Amplifying information for CVD. Recent (within 30 days) blood pressure reading. Results of a treadmill exercise test taken within one year, including an interpretation of the result by either a doctor or cardiologist

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
			is required.
Hypertension	Blood pressure >155/95 is disqualifying Applies to all classes of airmen	No specific standards or guidelines.	Original deck and engineer officer: Blood pressure higher than 150/90 is disqualifying (regardless of treatment with medication). Renewal or raise in grade of deck and engineer officer licenses: Blood pressure higher than 160/100 of under age 50, or 175/100 if over age 50 and on medication.
Myocardial Infarction	No medical history or current clinical diagnosis of myocardial infarction.	No specific standards or guidelines.	No history of multiple myocardial infarctions.
Thrombosis	Certification for applicants with thromboembolitic disease is described under Disease Protocols.	No specific standards or guidelines.	No specific standards or guidelines.

* Source of information for FAA Regulations and Guidelines: http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/dec_cons/disease_prot/hypertension/
† Source of information for Federal Railroad Administration Guidelines: http://www.fra.dot.gov/us/content/1586
‡ Source of information for Merchant Mariner Guidelines: http://www.uscgmil/hq/g-m/nvic/2_98/n2-98.pdf (NVIC 02-98)
CVD Cardiovascular disease.
FAA Federal aviation administration.
NYHA New York heart association.

Regulatory Medical Fitness Standards in Australia, Canada, and the United Kingdom

Regulatory standards and guidance pertaining to CVD and CMV driving in Australia, Canada, and the United Kingdom are presented in Table 14.

Table 14. Regulations Pertaining to CVD and CMV Driving from Selected Countries

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Angina	The criteria for an unconditional license are NOT met: • If the person is subject to angina pectoris. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review, in the following circumstances: • If a Bruce Treadmill Test (or equivalent protocol) of greater than 9 minutes (men) and 6 minutes (women) and thallium or sestamibi scan show no evidence of myocardial ischemia. • If myocardial ischemia is demonstrated, then a coronary angiogram may be offered. If that shows lumen diameter reduction of less than 70% in a major coronary branch, and less than 50% in the left main coronary artery, the person may be granted a conditional license, subject to annual review. If the result of the angiogram shows a lumen diameter reduction of equal to or greater than 70% in a major coronary branch and less than 50% in the left main coronary artery (or if an angiogram is not conducted) the person may be granted a conditional license: • if the clinical history is one of minimal symptoms; and • there is an exercise tolerance of greater than 9 minutes (men) and 6 minutes (women) on the Bruce Treadmill Test (or equivalent protocol); and • there is no evidence of severe ischemia, i.e., less than 2 mm ST segment depression on an exercise ECG and absence of a large defect on a stress perfusion scan; and • there is an ejection fraction of 40% or over. The presence of other risk factors should also be considered. Where surgery or angioplasty is undertaken to relieve the angina, the criteria listed in the table below apply.	Stable angina pectoris: No restrictions. Unstable angina pectoris: Waiting period 3 months.	Refusal or revocation with continuing symptoms (treated and/or untreated) Relicensing may be permitted when free from angina for at least 6/52, provided that the exercise/functional test requirements can be met and there is no other disqualifying condition.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Angioplasty (elective)	The person should not drive for at least 4 weeks after the angioplasty. The criteria for an unconditional license are NOT met: • if the person has had coronary angioplasty. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review: • at least 4 weeks after the angioplasty; • if the clinical history is one of minimal symptoms; and • there is an exercise tolerance of greater than 9 minutes (men) and 6 minutes (women) on the Bruce Treadmill Test (or equivalent protocol); and • there is no evidence of severe ischemia, i.e., less than 2 mm ST segment depression on an exercise ECG and absence of a large defect on a stress perfusion scan; and • there is an ejection fraction of 40% or more.	Waiting period 7 days. Reassessment at 6 months with clinical evaluation and exercise test.	Disqualifies from driving for at least 6/52. Relicensing may be permitted thereafter provided that the exercise/functional test requirements can be met and there is no other disqualifying condition.
CABG	The person should not drive for at least 3 months after CABG. The criteria for an unconditional license are NOT met: • following CABG. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to annual review: • at least 3 months after CABG. • if angina pectoris and dyspnea are absent on mild exertion; and • there is minimal residual musculoskeletal pain after the chest surgery; and • there is no other cardiac condition as per this publication which would render the person unfit to drive.	Waiting period 3 months.	Disqualifies from driving for at least 3 months. Relicensing may be permitted thereafter provided that the exercise/functional test requirements can be met on a test carried out no sooner than 3 months post-operatively and there is no other disqualifying condition. In addition the LVEF must be ≥40%.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Left Ventricular Assist Devices	Not addressed	Not addressed	Permanently bars
Acute coronary syndromes (ACS) including myocardial infarction	The person should not drive for at least 3 months after an AMI. The criteria for an unconditional license are NOT met: • If the person has had an AMI. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review: • At least 3 months after an uncomplicated AMI. • if the clinical history is one of minimal symptoms; and • there is an exercise tolerance of greater than 9 minutes (men) and 6 minutes (women) on the Bruce Treadmill Test (or equivalent protocol); and • there is no evidence of severe ischemia, i.e., less than 2 mm ST segment depression on an exercise ECG and absence of a large defect on a stress perfusion scan; and • there is an ejection fraction of 40% or over. The presence of other risk factors should also be considered. The nondriving period following a cardiac arrest should be determined by the treating specialist. The criteria for an unconditional license are NOT met: • if the person has suffered a cardiac arrest. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review, dependent on: • After an appropriate non-driving period; and • Depending on the cause of the cardiac arrest and response to treatment.	Waiting period 3 months.	ACS is defined for Group 2 license holders to include all acute coronary syndromes. These are all considered relevant and disqualify from driving for at least 6 weeks. Relicensing may be permitted thereafter provided that the exercise/functional test requirements can be met and there is no other disqualifying condition.
Carotid Artery Stenosis	Not addressed	Not addressed	If the level of stenosis is severe enough to warrant intervention, the exercise/functional test requirement must be met.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Peripheral Arterial Disease	Not addressed	Not addressed	Relicensing may be permitted provided that: there is no symptomatic myocardial ischemia, and the exercise test requirements can be met. When exercise testing cannot be completed to the required level, other functional testing or specialist cardiologic opinion may be required.
Ascending/Descending Thoracic Aortic Aneurysm and Abdominal Aortic Aneurysm	The person should not drive for at least 3 months post-repair. The criteria for an unconditional license are NOT met: • if the person has aortic aneurysm, thoracic, or abdominal. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of an appropriate specialist, and the nature of the driving task, and subject to periodic review: • at least 3 months after repair; • if the condition is minor; or • if the condition has been adequately treated.	Not addressed	Disqualifies from driving if the aortic diameter is >5.5 cm. Driving may continue after satisfactory medical or surgical treatment, unless other disqualifying condition. NB Exercise/functional test requirement will apply for abdominal aortic aneurysm.
Arrhythmias • **Sinoatrial disease** • **Significant atrio-ventricular conduction defect** • **Atrial flutter/fibrillation** • **Narrow or broad complex tachycardia** **NB: Transient Arrhythmias occurring during acute coronary syndromes do not require assessment under this section.**	The criteria for an unconditional license are NOT met: • if the person has a history of recurrent or persistent arrhythmia, which may result in syncope or incapacitating symptoms. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review: • if the condition has been cured surgically (e.g., Wolf-Parkinson-White syndrome); or • if the condition has been successfully treated medically for at 3 three months; or • if the person is taking anticoagulants refer to anticoagulant therapy above.	All cases of ventricular fibrillation and VT are disqualified. Nonsustained paroxysmal VT Paroxysmal supraventricular tachycardia Paroxysmal atrial flutter or fibrillation with no associated cerebral ischemia and no underlying heart disease – no restriction. Nonsustained paroxysmal VT Paroxysmal supraventricular tachycardia Paroxysmal atrial flutter or fibrillation with ventricular pre-excitation and no associated cerebral ischemia – must demonstrated adequate control. Nonsustained paroxysmal VT Paroxysmal supraventricular tachycardia Paroxysmal atrial flutter or fibrillation with associated cerebral ischemia or underlying heart disease - must demonstrated adequate control. Sinus node dysfunction (sick sinus syndrome, sinus bradycardia, sinus exit block, sinus arrest) – No pauses >3 s on Holter monitoring.	Disqualifies from driving if the arrhythmia has caused or is likely to cause incapacity. Driving may be permitted when the arrhythmia is controlled for at least 3/12, provided that the LVEF is satisfactory (i.e., LVEF is ≥0.4), and there is no other disqualifying condition.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Pacemaker Implant	The person should not drive for at least 1 month after insertion of pacemaker. The criteria for an unconditional license are NOT met: • If a cardiac pacemaker is required. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of the treating doctor/GP, and the nature of the driving task, and subject to periodic review: • at least 2 weeks after insertion of the cardiac pacemaker; and • if no other condition renders driver unfit to drive.	Waiting period one month No cerebral ischemia Normal sensing and capture on ECG Device performing within manufacturer's specifications Pacemaker output pulse ≥2 times stimulation threshold	Disqualifies from driving for 6/52. Relicensing may be permitted thereafter provided there is no other disqualifying condition.
Successful Catheter Ablation	Not addressed	Not addressed	Disqualifies from driving for 6/52. Relicensing may be permitted thereafter provided that there is no other disqualifying condition.
Unpaced Congenital Complete Heart Block	Not addressed	Not addressed	Bars whether symptomatic or asymptomatic.
Atrial Defibrillator (physician/patient activated)	Not addressed	Not addressed	Relicensing may be permitted provided that the arrhythmia section is met and there is no other disqualifying condition.
Atrial Defibrillator (Automatic)	Not addressed	Not addressed	Permanently bars

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
ECG Abnormality	An ECG is not routinely required for commercial vehicle driver examinations and should only be undertaken if clinically indicated. The criteria for an unconditional license are NOT met: • if the person has an electrocardiographic abnormally, for example left or right bundle branch block, pre-excitation or changes suggestive of myocardial ischemia or previous myocardial infarction. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to annual review: • if the condition has been cured surgically; or • if the condition has been successfully treated medically for at least 3 months; or • there is an exercise tolerance of greater than 9 minutes (men) and 6 minutes (women) on the Bruce Treadmill Test (or equivalent protocol); and • there are no other disqualifying conditions. (See also pacemakers).	Not addressed	Relicensing may be permitted provided that there is no other disqualifying condition and the exercise test requirements can be met.
Left Bundle Branch Block	Not addressed	Not addressed	Relicensing may be permitted provided that there is no other disqualifying condition and the functional test requirements can be met.
Ventricular Preexcitation	Not addressed	Satisfactory control must be demonstrated.	May be ignored unless associated with an arrhythmia or another disqualifying condition.
Implantable Cardioverter Defibrillator (ICD) implanted for ventricular arrhythmia associated with incapacity	The criteria for an unconditional license are NOT met: • if the person has a cardiac defibrillator implanted for ventricular arrhythmias.	Not addressed	Permanently bars
ICD implanted for sustained ventricular arrhythmia which did not cause incapacity	The criteria for an unconditional license are NOT met: • if the person has a cardiac defibrillator implanted for ventricular arrhythmias.	Not addressed	Permanently bars
Prophylactic ICD Implant	Not addressed	Not addressed	Permanently bars
Arrhythmogenic Right Ventricular Dysplasia (ARVD) and allied disorders (See also arrhythmia, pacemaker, and ICD sections)	Not addressed	Not addressed	Asymptomatic– Driving must cease but may be permitted following specialist electrophysiologic assessment provided that there is no other disqualifying condition. Symptomatic– permanently bars

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Syncope *1. Simple Faint* Definite provocational factors with associated prodromal symptoms and which are unlikely to occur whilst sitting or lying. Benign in nature. If recurrent, will need to check the 3 "Ps" apply on each occasion (provocation/prodrome/postural)	Not addressed	There is no need to restrict the driving privileges of such a patient.	No driving restrictions DVLA need not be notified.
2. *Loss of consciousness/ loss of or altered awareness likely to be unexplained syncope and low risk of reoccurrence.* These have no relevant abnormality on CVS and neurologic examination and normal ECG.	The person should not drive for 6 months following unexplained syncope. The criteria for an unconditional license are NOT met: • if the person suffers from unheralded recurrent syncope/blackouts that do not respond to treatment.	Single episode: Waiting period 3 months >1 episode in 1 year: Waiting period 12 months	Can drive 3 months after the event.
3. *Loss of consciousness/ loss of or altered awareness likely to be unexplained syncope and high risk of re-occurrence* Factors indicating high risk: (a) Abnormal ECG (b) Clinical evidence of structural heart disease (c) Syncope causing injury, occurring at the wheel or whilst sitting or lying (d) >1 episode in previous six months.	The person should not drive for at least 3 months after syncope. The criteria for an unconditional license are NOT met: • if the condition is severe enough to cause episodes of loss of consciousness without warning. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of an appropriate specialist, and the nature of the driving task, and subject to at least annual review depending on: • identification of the underlying cause; and/or • the institution of satisfactory treatment.	Single episode: Waiting period 3 months >1 episode in 1 year: Waiting period 12 months	Can drive after 3 months if the cause has been identified and treated. If no cause identified, then license refused/revoked for one year.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Hypertension	People with hypertension consistently less than 200/110 (treated or untreated) may drive without license restriction and without notification to the DLA. They should be reviewed by their treating doctor periodically regarding progression of the illness. The criteria for an unconditional license are NOT met: • if the person's sitting blood pressure is consistently 200/110 or greater (treated or untreated); or • if there is end-organ damage (cardiac, cerebral, or retinal) which will impair safe driving; or • if treatment results in marked postural hypotension or impaired alertness. The presence of other factors should also be considered. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to annual review: • If the person is treated with antihypertensive drug therapy and effective control of hypertension is achieved (ideal blood pressure less than 140/90 but no greater than 150/95) without appreciable side effects over a four week follow-up period; and • If there is no evidence of damage to target organs relevant to driving, or associated ischemia, or other forms of heart disease; and • If causative factors have been treated.	Hypertension, other than uncontrolled malignant hypertension, is not by itself considered to be a contraindication to the operation of any class of motor vehicle. However, because of the associated consequences of high blood pressure of 170/110 or higher, ECG, chest radiography, funduscopic examination and a BUN should be performed. If the individual with hypertension over 170/110 is unable to reduce their blood pressure to a level below this figure they should not be recommended for licensing as professional drivers (classes 1–4).	Disqualifies from driving if resting BP consistently 180 mmHg systolic or more and/or 100 mmHg diastolic or more. Relicensing may be permitted when controlled provided that treatment does not cause side effects which may interfere with driving.
Chronic Aortic Dissection	Not addressed	Not addressed	Re/licensing may be permitted if ALL of the following apply: maximum transverse diameter of the aorta, including false lumen/thrombosed segment, does not exceed 5.5 cm; there is complete thrombosis of the false lumen; BP is well controlled* NOTE "well controlled" refers to clinical, NOT DVLA, standard of control.
Marfan Syndrome	Not addressed	Not addressed	Relicensing permitted subject to the requirements for aneurysm being met (q.v.), satisfactory medical treatment, and annual cardiac review to include aortic root measurement. NOTE that aortic root replacement will debar.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Hypertropic Cardiomyopathy (HCM)	The criteria for an unconditional license are NOT met: • if the person has HCM. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review: • if the person is asymptomatic; and • LVEFis 40% or over; and • the person is able to complete 9 minutes (men) 6 minutes (women) of the Bruce Treadmill Test (or equivalent) without significant cardiac symptoms or significant ST segment (>2 mm) shift; and • There is an absence of severe LV hypertrophy, a family history of sudden death, or ventricular arrhythmia on Holter testing.	Disqualified unless: • functional class I; • no associated cerebral ischemia; • Holter class II; • LV outflow tract gradient ≤30 mmHg at rest as assessed by Doppler or cardiac catheterization.	Disqualifies from driving if symptomatic. Licensing may only be permitted where at least 3 of the following criteria are met: 1) There is no family history in a first degree relative of sudden premature death from presumed HCM; 2) The cardiologist can confirm that the HCM is not anatomically severe. There should be no more than 3 cm maximum wall thickness; 3) There is no serious abnormality of heart rhythm demonstrated (e.g., ventricular tachyarrhythmia excluding isolated ventricular preexcitation beats). It is demonstrated that there is at least 25mm Hg increase in systolic blood pressure occurring during the completion of 9 minutes of exercise testing.
Dilated Cardiomyopathy (See also arrhythmia, pacemaker, ICD and heart failure sections)	Not directly addressed	Disqualified unless: • Functional class I • No associated cerebral ischemia • Holter class II • LV outflow tract gradient ≤30 mmHg at rest as assessed by Doppler or cardiac catheterization	Disqualifies from driving if symptomatic. Relicensing may be permitted provided that there is no other disqualifying condition.
Heart and Lung Transplant	The person should not drive for at least 3 months posttransplant. The criteria for an unconditional license are NOT met: • If the person has had a heart or heart/lung transplant. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a transplant cardiologist, and the nature of the driving task, and subject to at least annual review: • at least 3 months after transplant.	Waiting period 6 months Functional class I LV class I or LV class II + Holter class II	Disqualifies from driving if symptomatic. Relicensing may be permitted provided that the exercise/functional test requirement can be met, the LV function remains good (i.e., LVEF is ≥0.4) and there is no other disqualifying condition.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Heart Valve Disease (to include surgery, i.e., replacement and/or repair)	The criteria for an unconditional license are NOT met: • if the person has any history or evidence of valve disease, with or without surgical repair or replacement, association with symptoms or a history of embolism, arrhythmia, cardiac enlargement (on chest x-ray greater than 16 cm), abnormal ECG, high blood pressure; or • if the person is taking anticoagulants; or • if mitral stenosis is present with echocardiograph evidence of moderate (valve area <1.5 cm^2) or severe stenosis. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to annual review: • if the person's cardiologic assessment shows mild valvular disease of no hemodynamic significance, and there is no other cardiac condition as per this publication which would render the person unfit to drive; or • 3 months following successful surgery and there is no other cardiac condition as per this publication which would render the person unfit to drive.	Aortic stenosis. Allowed to drive if: • Asymptomatic • Functional class I • Estimated aortic valve area >1.0 cm^2 assessed by echocardiography or cardiac catheterization • LV class I or LV class II+ Holter class II Aortic regurgitation, mitral stenosis, or mitral regurgitation. Allowed to drive if: • No associated cerebral • Ischemia • Functional class I • LV class I or • LV class II + Holter class II Mechanical prostheses mitral bioprosthesis or valvuloplasty with nonsinus rhythm: • Waiting period 3 months • No thromboembolic complications • Functional class I • LV class I or • LV class II + Holter class II • Anticoagulant therapy Aortic bioprosthesis, mitral bioprosthesis or valvuloplasty with sinus rhythm: • No thromboembolic complications • Functional class I • LV class I or LV class II + Holter class II • Waiting period 3 months	Disqualifies from driving: 1) Whilst symptomatic. 2) For 12 months after cerebral embolism following which specialist assessment is required to determine licensing fitness. Relicensing may be permitted provided there is no other disqualifying condition.

Cardiovascular Disorder	Australia*	Canada†	United Kingdom‡
Heart Failure	The criteria for an unconditional license are NOT met: • if the person has heart failure. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to annual review: • if there is an exercise tolerance of greater than 9 minutes (men) and 6 minutes (women) on the Bruce Treadmill Test (or equivalent protocol); and • there is an ejection fraction of 40% or over; and • there is a satisfactory response to treatment; and • the underlying cause of the heart failure is considered.	Functional class I. Allowed to drive if: • LV class I or LV class Holter class II Functional class II and III: Disqualified	Disqualifies from driving if symptomatic. Relicensing may be permitted provided that the LVEF is good (i.e., LVEF is ≥0.4), the exercise/functional test requirements can be met and there is no other disqualifying condition.
Congenital Heart Disease	The criteria for an unconditional license are NOT met: • if the person has a complicated congenital heart disorder. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a cardiologist, and the nature of the driving task, and subject to periodic review: • if there is a minor congenital heart disorder such as pulmonary stenosis, atrial septal defect, small ventricular septal defect, bicuspid aortic valve, patent ductus arteriosis, or mild coarctation of the aorta; and • there are no other disqualifying conditions.	No diagnosis-specific recommendations are made. Assessment should be based on the presence or absence of myocardial ischemia, left ventricular dysfunction, valvular lesions, and/or disturbances of cardiac rhythm, and should adhere to the relevant guidelines.	Disqualifies from driving when complex or severe disorder(s) is (are) present. On first application/identification a recent examination /assessment by an appropriate consultant will be required before a license is issued. Those with minor disease and others who have had successful repair of defects or relief of valvular problems, fistulae, etc. may be licensed provided that there is no other disqualifying condition. Certain conditions will require the issue of a medical review license for 1, 2, or 3 years.
Deep Vein Thrombosis	The nondriving period following DVT should be determined by the treating specialist. The criteria for an unconditional license are NOT met: • if the person has deep vein thrombosis which is liable to recurrence or embolus. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a specialist, and the nature of the driving task, and subject to periodic review: • following an appropriate non-driving period; and • depending on the cause of the thrombosis and the response to treatment.	Not addressed	Not addressed

* Source of information for Australia: http://www.austroads.com.au/aftd/index.html

† Source of information for Canada: http://www.cma.ca/index.cfm/ci_id/18223/la_id/1.htm
‡ Source of information for U.K. http://www.dvla.gov.uk/medical.aspx?keywords=medical

ACS	Acute coronary syndrome.
AMI	Acute myocardial infaction.
BP	Blood pressure.
BUN	Blood urea nitrogen.
CABG	Coronary artery bypass grafting.
CVS	Cardiovascular system.
DLA	Driver licensing authority.
DVLA	Driver and vehicle licensing agency.
DVT	Deep-vein thrombosis.
ECG	Electrocardiogram.
GP	General practitioner.
HCM	Hypertropic cardiomyopathy.
ICD	International classification of diseases.
LV	Left ventricle.
LVEF	Left ventricular ejection fraction.
ST	Sinus tachycardia.
VT	Ventricular tachycardia.

Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for this evidence report. The section briefly covers the key questions addressed, literature searches performed, the criteria used including studies, an evaluation of study quality, an assessment of the strength of the evidence base for each key question, and the methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, and statistical approaches used are documented in appendices.

Key Questions

This evidence report addresses six key questions. Each one was developed by FMCSA so that their answers would provide information that is useful in aiding the agency with updating their current medical examination guidelines titled, "Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Drivers."(1) The six key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with CVD at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What are the risk factors for rupture of an aortic (abdominal or thoracic) aneurysm?

Key Question 3: Is implantation of a pacemaker effective in preventing vasovagal syncope recurrence?

Key Question 4: What is the risk of sudden incapacitation or sudden death following implantation of an ICD?

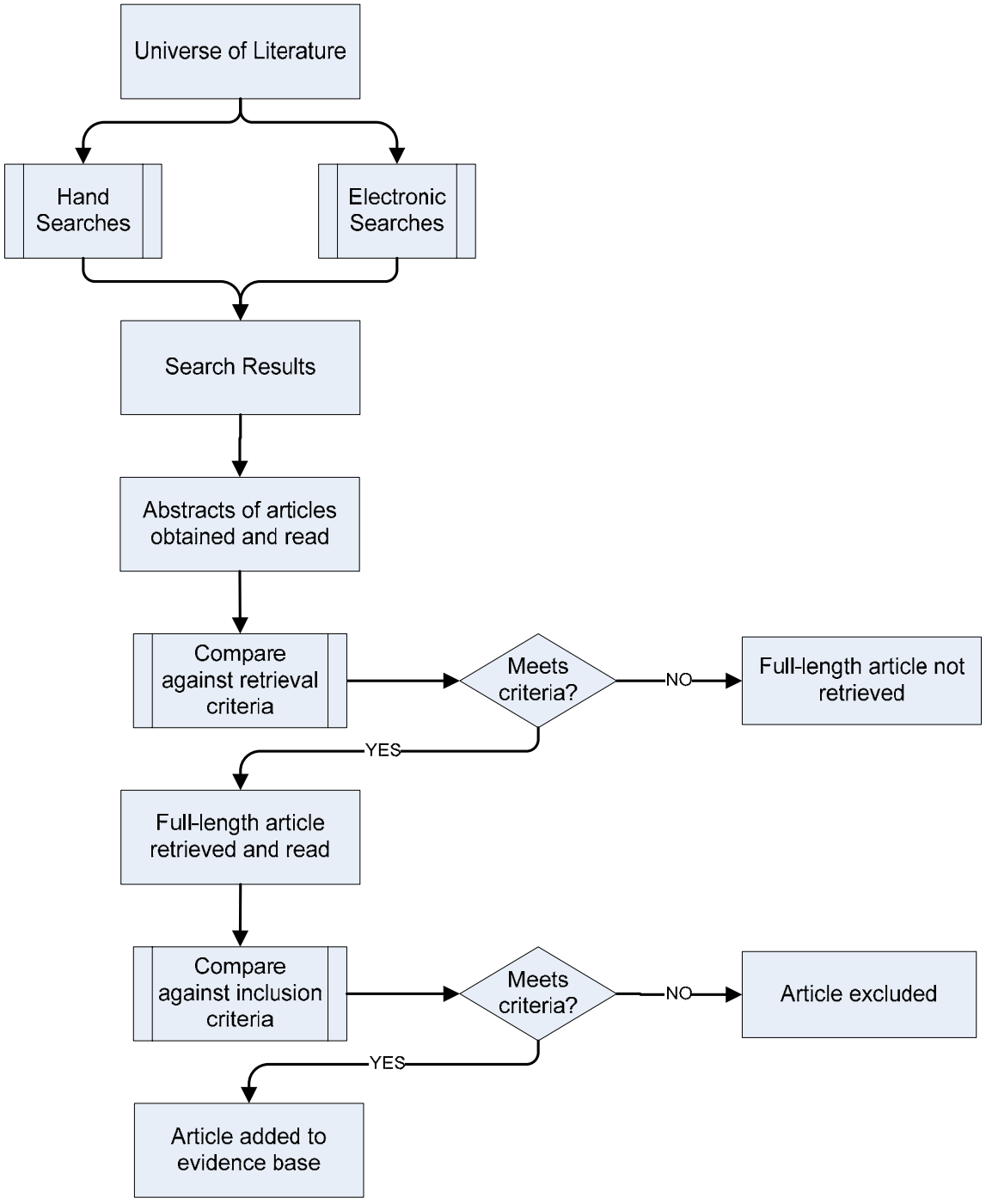
Key Question 5: What is the risk for sudden death or incapacitation in individuals with low LVEF (<50%, <40%, <35%)?

Key Question 6: Is the relationship between LVEF and sudden death or incapacitation (if established) dependent on the underlying etiology of heart failure?

Identification of Evidence Bases

The individual evidence bases for each of the six key questions addressed in this evidence report were identified using the multistaged process captured by the algorithm presented in Figure 1. The first stage of this process consists of a comprehensive search of the literature. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles will be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

Figure 1. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews that use a less rigorous approach to identifying and obtaining literature, which allows a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias, because we obtain and include articles according to explicitly determined *a priori* criteria. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 15.

Table 15. Electronic Databases Searched

Name of Database	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	Through November 28, 2006	OVID
Cochrane Library	Through November 28, 2006	http://www.thecochranelibrary.com
EMBASE (Excerpta Medica)	Through November 28, 2006	OVID
Medline	Through November 28, 2006	OVID
PubMed (PreMEDLINE)	Through November 28, 2006	http://www.pubmed.gov
TRIS Online (Transportation Research Information Services Database)	Through November 28, 2006	http://trisonline.bts.gov/search.cfm

Manual Searches

We reviewed journals and supplements maintained in ECRI's collections of more than 1,000 periodicals. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. In order to retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies,

private organizations, educational facilities, consulting firms, and corporations. The latter documents do not appear in the peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions pertaining to whether a full-length article should be retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with FMCSA. The retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), it was unclear whether the full-length version of that article was to be obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI analyst who determined whether it article met a set of predetermined, question specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion criteria for this evidence report were determined *a priori* in conjunction with FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article it was found not to meet the question-specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, are presented in Appendix D.

Evaluation of Quality and Strength of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence that was used to draw an evidence-based conclusion.(52) Using this approach, which is described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., "Individuals with CVD are at increased risk for a motor vehicle crash") and a quantitative conclusion (e.g., "When compared to individuals who do not have CVD, the risk ratio for a motor vehicle crash among individuals with the disorder is 1.37; 95% CI: 1.03–1.74; *P* <0.005."). As shown in Table 16, we assigned a separate strength-of-evidence rating to each type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect-size estimate that was calculated.

Table 16. Strength-of-Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect-Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by minimally acceptable evidence. Likewise, quantitative effect-size estimates that were deemed stable are more unlikely to change significantly with the publication of new data than are unstable effect-size estimates.

Statistical Methods

The set of analytic techniques used in this report was extensive. In summary, random- and fixed-effects meta-analyses were used to pool data from different studies.(2-6,53,54) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(7-9,53,55-57) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(58-60) Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative fixed- and random-effects meta-analyses.(10-12,61-64) The presence of publication bias was tested for using the "trim and fill" method.(65) All meta-analyses in this evidence report were performed using Comprehensive Meta-Analysis software.(13-15)

We calculated several different estimates of effect. The choice of effect-size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or the data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using either the rate ratio (RR) or the odds ratio (OR). Time-to-event data were analyzed using the hazard ratio (HR). The formulaes for these effect sizes and their variance are presented in Table 17. If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(66)

Table 17. Effect-size Estimates Used in Evidence Report and their Variance

Effect Size	Formula (Effect size)	Formula (Variance)
WMD	$\mu_{TG}-\mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}}+\frac{1}{n_{cg}}\right)$
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); s_{TG} = standard deviation (treatment group); s_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
Event Rate	$a/a+b$	$\ln\left[\frac{1}{a}+\frac{1}{a+b}\right]$
Where: a = number of individuals in cohort experiencing an event; b = number of individuals in cohort who did not experience an event		
RR (incidence)	$\left(\frac{a_{CVDs}}{pt_{CVD}}\right)\Big/\left(\frac{b_{control}}{pt_{control}}\right)$	$\ln\left[\frac{1}{a_{CVD}}+\frac{1}{b_{control}}\right]$
Where: a = number of individuals with CVD who crashed; pt_{CVD} = rate denominator (CVD grp); b = number of individuals without CVD who crashed; $pt_{control}$ = rate denominator (control grp)		

Effect Size	Formula (Effect size)	Formula (Variance)
OR	$\left(\frac{a}{b}\right) \Big/ \left(\frac{c}{d}\right) = \left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$
RR	$\left(\frac{a}{a+c}\right) \Big/ \left(\frac{b}{b+d}\right)$	$\frac{1}{a}+\frac{1}{a+c}+\frac{1}{b}+\frac{1}{b+d}$
Where: a = number of individuals with CVD who crashed; b = number of individuals without CVD who crashed; c = number of individuals with CVD who did not crash; d = number of individuals without CVD who did not crash.		
HR	$\frac{O_{pi}/E_{pi}}{O_{ci}/E_{ci}}$	$\exp\left(\ln\left[\frac{1}{E_{pi}}+\frac{1}{E_{ci}}\right]\right)$
Where O_{pi} = observed number of events in treatment group; O_{ci} = observed number of events in control group; E_{pi} = logrank expected number of events in treatment group; E_{ci} = logrank expected number of events in control group		

CVD Cardiovascular disease.
HR Hazard ratio.
OR Odds ratio.
RR Rate ratio.
SMD Standardized mean difference.
WMD Weighted mean difference.

Synthesis of Results

This section summarizes the findings of our systematic review of the evidence pertaining to each of the key questions that we addressed in this evidence report.

Key Question 1: Are individuals with CVD[4] at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Background

Due to its prevalence, CVD is a particular concern to those responsible for road safety (see *Background*). Approximately half of all individuals who experience a heart attack will die—often suddenly—with many individuals who develop an MI experiencing rapid incapacitation. SCD or incapacitation while driving a CMV clearly represents a safety hazard. The most likely cause of sudden death or incapacitation is arrhythmia resulting from CHD. Other less common cardiovascular conditions that may lead to sudden death or incapacitation include benign arrhythmias (which cause syncope in up to one third of those affected), transient AV block, sinoatrial disorder, malignant vasovagal syncope, and rupture of an AAA.

The term "sudden" as it is applied to cardiac death or incapacitation is often misconstrued as meaning instantaneous. While death or incapacitation may be sudden, it is in fact rarely instantaneous. Most individuals will experience at least some warning to indicate the onset of the event. Thus, not all individuals who experience sudden death or incapacitation while driving will crash. Evidence in the form of reports of individuals found dead in cars demonstrate that at least some individuals do have enough time to pull off the road before they die.(67-72) Indeed, several authorities have argued that sudden death or incapacitation while driving that leads to injury to others is extremely rare and does not pose a serious threat to road safety.(72) For example, a 1983 report from the Canadian

[4] With an emphasis on crash risk associated with myocardial infarction, angina pectoris, coronary insufficiency and thrombosis

Cardiovascular Committee stated the following: "It is somewhat surprising to learn that heart disease in motor vehicle drivers emerges as only a minor problem in traffic safety. Crashes caused by drivers incapacitated by CVD are uncommon, but it is even rarer still for [someone] other than the stricken driver himself to be injured or killed as a result of an ensuing crash."(73)

Previous reviews of the literature note that the available literature on crash risk associated with CVD is inconsistent.(26,74,75) However, none of these reviews have formally assessed the studies they cite using the methodology of systematic review and meta-analysis. In this section of the evidence report, we utilize these methods to synthesize the available evidence pertaining to crash risk among individuals with CVD. The aim of our analysis is to empirically determine whether individuals with CVD are at higher risk for a crash than individuals who do not have the disease and, if an increased risk is observed, to quantify the magnitude of this excess risk.

Identification of Evidence Base

To meet the aims of this section of the evidence report, we searched for comparative trials that compared crash risk among individuals with CVD and otherwise comparable individuals who do not have the disorder.

The identification of the evidence base for Key Question 1 is summarized in Figure 2. Our searches[5] identified a total of 451 articles that appeared relevant to this key question. Following application of the retrieval criteria for this question, 47 full-length articles were retrieved and read in full. Fifteen of these 47 retrieved articles were found to meet the inclusion criteria[6] for Key Question 1 (Table 18). Table D-1 of Appendix D lists the 32 articles that were retrieved but then excluded. The table also provides the reason for their exclusion.

[5] See Appendix A for search strategies

[6] See Appendix C for inclusion criteria

Figure 2. Development of Evidence Base for Key Question 1

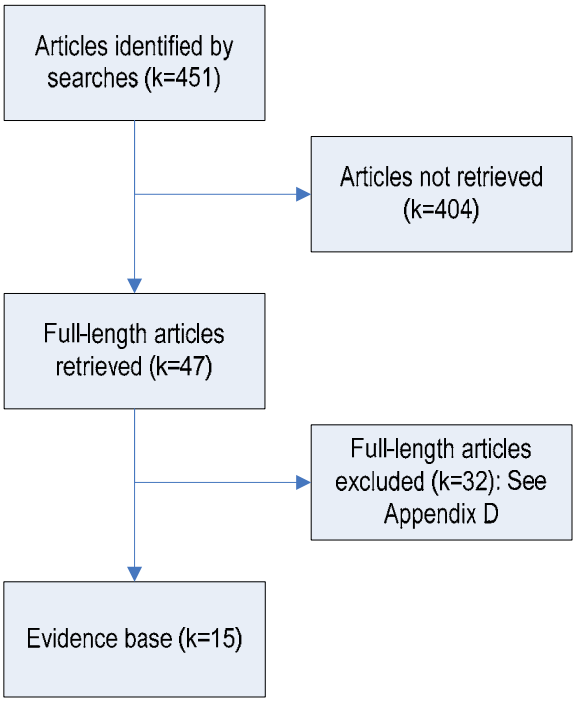


Table 18. Evidence Base for Key Question 1

Primary Reference	Year	Secondary References	Study Location	Country
Vernon et al.(76)	2002		Salt Lake City, Utah	USA
McGwin et al.(77)	2000	McGwin et al.(78)	Mobile County, Alabama	USA
Jovanovic et al.(79)	1999	Jovanovic et al.(80) Jovanovic et al.(81)	Nis, Yugoslavia	Yugoslavia (now Serbia and Montenegro)
Guibert et al.(82)	1998		Quebec	Canada
Dionne et al.(17)	1995	Dionne et al.(83) Laberge-Nadeau et al.(84)	Quebec	Canada
Medgyesi et al.(16)	1995		Regina, Saskatchewan	Canada
Gresset and Meyer(85)	1994		Quebec	Canada
Koepsell et al.(86)	1994		Puget Sound, Washington	USA
Naughton et al.(87)	1982		Chittenden County, Vermont	USA
Davies et al.(88)	1973	Davies and Wehling(89)	Oklahoma City Department of Public Safety, Oklahoma	USA

Primary Reference	Year	Secondary References	Study Location	Country
Crancer and O'Neall(90)	1970		Department of Motor Vehicles, Seattle, Washington	USA
McMurray and Crancer(91)	1968		Department of Motor Vehicles, Seattle, Washington	USA
Waller(92)	1967		Rossmoor Leisure World, Seal Beach, California	USA
Ysander(93)	1966		County Hospital, Varberg	Sweden
Waller(94)	1965		California Department of Motor Vehicles, California	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 15 studies that comprise the evidence base for Key Question 1. Here we discuss applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 19 and Table 20.

Table 19. Key Study Design Characteristics of Studies that Address Key Question 1

Reference	Year	Research Question	Subtype(s) of CVD Examined (if mentioned)	Study Design	Variables matched?	Comparison Assessed
Vernon et al.(76)	2002	Are motor vehicle crash rates among individuals with CVD higher than among individuals without the disorder?	Heart disease Arrhythmias Myocardial Infarction Heart surgery Hypertension	CCS	Age, sex, place of location, time frame	Crash rates among individuals with CVD vs. crash rates among healthy controls
McGwin et al.(77)	2000	Are individuals with CVD overrepresented among a cohort of individuals who crashed when compared to a cohort of individuals who did not crash?	Heart disease (nonspecific) Hypertension	CCS	Age, sex, year of crash, place of residence,	% of crashers with CVD (all types + subtypes) vs. % of noncrashers with CVD (all types + subtypes)
Jovanovic et al.(79)	1999	Are motor vehicle crash rates among individuals with CVD higher than among individuals without the disorder?	Coronary artery disease Arrhythmia Thromboangiitis obliterans Hypertension	CCS	None	Crash rates among individuals with CVD vs. crash rates among healthy controls
Guibert et al.(82)	1998	Are individuals with CVD overrepresented among a cohort of individuals who crashed when compared to a cohort of individuals who did not crash?	Coronary artery disease	CCS	Age, sex, place of residence, time frame of occurrence	% of crashers with CVD (all types + subtypes) vs. % of noncrashers with CVD (all types + subtypes)

Reference	Year	Research Question	Subtype(s) of CVD Examined (if mentioned)	Study Design	Variables matched?	Comparison Assessed
Dionne et al.(17)	1995	Are truck drivers with CVD overrepresented among a cohort of individuals who crashed when compared to a cohort of individuals who did not crash?	Coronary disease Hypertension	Nested-CCS	Mileage, sex, time frame, commercial truck driving	The effect of different medical conditions on truck drivers' distributions of crashes
Medgyesi et al.(16)	1995	Is CVD a significant medical impairment to driving?	Ischemic heart disease Pulmonary circulation disease Other heart disease	CCS	Controls were matched based on age (closest category possible), sex, population of place of residence, license class, and period of driving (time spent in the SGI program), and comorbid conditions.	Crash rates among individuals with CVD (vs. crash rates among healthy controls
Gresset and Meyer(85)	1994	Are individuals with CVD overrepresented among a cohort of individuals who crashed when compared to a cohort of individuals who did not crash?	Ischemic heart disease Arrhythmias Heart failure Hypertension	CCS	Age, location	% of crashers with CVD (all types + subtypes) vs. % of noncrashers with CVD (all types + subtypes)
Koepsell et al.(86)	1994	Are individuals with CVD overrepresented among a cohort of individuals who crashed when compared to a cohort of individuals who did not crash?	Coronary heart disease Arrhythmia Conduction abnormality Hypertension	CCS	Age, involvement in collision as driver, location	% of crashers with CVD (subtypes) vs. % of noncrashers with CVD (subtypes)
Naughton et al.(87)	1982	Do drivers with IHD have an increased crash risk when compared to age-sex-residence matched controls?	All types of IHD	CCS	Age, sex, miles driven, type of traffic	725 individuals with IHD compared to 725 age, sex, and residence matched individuals without IHD
Davies et al.(88)	1973	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	None specified	CCS	Sex, location of residence, time frame	55 individuals with CVD compared with 1,650,245 drivers in Oklahoma
Crancer and O'Neall(90)	1970	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	Arteriosclerosis Rheumatic Other heart disease Hypertension	CCS	Sex, age, city of residence	141 individuals with CVD compared with 141 age, sex, and city of residency matched individuals with no diagnosis of CVD
McMurray and Crancer(91)	1968	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	None specified	CCS	Sex and age, state of inhabitancy	7,416 individuals with CVD compared with 1,600,000 individuals without CVD
Waller(92)	1967	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	None specified	CCS	Age, CVD, signs of senility, mileage	35 individuals (≥60) with CVD compared to 37 "healthy" individuals (≥60 years old)

Reference	Year	Research Question	Subtype(s) of CVD Examined (if mentioned)	Study Design	Variables matched?	Comparison Assessed
Ysander(93)	1966	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	Valvular heart disease Coronary heart disease Other heart disease Hypertension	CCS	Age, sex, duration of having license	CVD (all types) vs. control
Waller(94)	1965	Are individuals with CVD at higher risk for a motor vehicle crash than individuals who do not have the disorder?	None specified	CCS	Age, state of residence, miles driven	2,672 consecutive people with known chronic medical conditions whose records were under review by the Department of Motor Vehicles. Controls (926) were from a random sample of California drivers (total = 7,500) who filled out a questionnaire given to all renewal applications on June 6, 1963.

CCS Case-control study.
CVD Cardiovascular disease.
IHD Ischemic heart disease.

All of the included studies used one of two different case-control methodologies. The most commonly used methodology (*k = 11*) was to select drivers with CVD (cases) and compare their risk with that of drivers not having the condition. The less commonly used, alternate approach was to select cohorts on the basis of crash involvement and to compare the prevalence of CVD among individuals who experienced a crash (cases) and those who did not (controls) (*k = 4*).

Table 20. Outcomes Assessed by Studies that Address Key Question 1

Reference	Year	Primary Outcome	Attempt made to control for exposure?	Definition of Crash	Outcome self-reported?
Vernon et al.(76)	2002	Rates of adverse driving events (crash, at-fault crash, and citations) experienced by drivers licensed with medical conditions to controls.	Time frame - Yes Mileage – No Type of roads – No	Motor vehicle crashes, at-fault crashes, violations	No – all data were obtained through records.
McGwin et al.(77)	2000	Medical conditions and medications associated with risk of at-fault crashes among older drivers.	Time frame - Yes Mileage – No Type of roads – No	At-fault motor vehicle collisions	Yes– although crash data obtained from police records, medical information was obtained by telephone interview.
Jovanovic et al.(79)	1999	Prevalence and influence of cardiovascular disorders on the occurrence of traffic crashes.	Time frame - No Mileage – No Type of roads – No	Any motor vehicle crash	No – police data and medical records were used.
Guibert et al.(82)	1998	Whether drivers with CVD are more likely to be involved in motor vehicle crashes (MVCs).	Time frame - Yes Mileage – No Type of roads – No	Motor passenger vehicle collision	Yes – questionnaire based.
Dionne et al.(17)	1995	The effect of different medical conditions, including CVD, on truck drivers' distributions of crashes.	Time frame - Yes Mileage – Yes Type of roads – Yes	Truck collision	No – data on health was collected for drivers with medically restricted licenses through their records. Other

Reference	Year	Primary Outcome	Attempt made to control for exposure?	Definition of Crash	Outcome self-reported?
					data was collected by interview.
Medgyesi et al.(16)	1995	Crash rates of persons with CVD compared to controls.	Time frame - Yes Mileage – No Type of roads – No	Motor vehicle crash	No
Gresset and Meyer(85)	1994	The influence of medical conditions, including heart disease, on crash risk.	Time frame - Yes Mileage – No Type of roads – No	Crashes without serious injuries or fatalities	Yes – data on crashes were collected through records, but data on medical conditions were self-reported.
Koepsell et al.(86)	1994	Injury due to motor vehicle collision in older drivers.	Time frame - Yes Mileage – No Type of roads – No	Motor vehicle collision	No
Naughton et al.(87)	1982	Whether drivers with ischemic heart disease (IHD) have an increased crash risk.	Time frame - Yes Mileage – Yes Type of roads – Yes	Cases from crashes admitted to hospital	No
Davis et al.(88)	1973	To assess "fitness to drive" of drivers in collisions.	Time frame - Yes Mileage – No Type of roads – No	Crashes and moving violations	No
Crancer and O'Neall(90)	1970	If drivers with disease have significantly higher crash, violation, or crash and violation rates.	Time frame - Yes Mileage – No Type of roads – No	Crash, violation, and crash plus violation	No
McMurray and Crancer(91)	1968	Crash and violation rates of medically restricted drives.	Time frame - Yes Mileage – No Type of roads – No	Crash or moving violation	No
Waller(92)	1967	Crash risk	Time frame - Yes Mileage – Yes Type of roads – No	Crashes and traffic violations	Yes – surveys were collected in addition to driving records.
Ysander(93)	1966	To determine to what extent a disease or related therapy are associated with crashes or traffic offenses; If drivers with a given disease are at higher risk for crash or offenses; If drivers with chronic disease are over-represented in road crashes and offenses.	Time frame - Yes Mileage – No Type of roads – No	Investigated injurious crashes and offenses	No
Waller(94)	1965	To investigate whether drivers with known medical conditions (include CVD) have higher traffic crash and violation rates.	Time frame - Yes Mileage – Yes Type of roads – No	Crash and violations	No

CVD Cardiovascular disease.
IHD Ischemic heart disease.
MVCs Motor vehicle crashes.

A design problem common to many risk assessment studies is the failure to control adequately for exposure. In this instance, the exposure variables of critical importance are the number of miles driven per unit time, the time frame over which data were collected, and the type(s) of roads driven on. If cases and controls are not well matched for exposure to risk, then any observed differences in the risk may simply be the consequence of differences in exposure. Although

most included studies attempted to control for at least one of these three exposure variables, only two attempted to control for all three—Dionne et al.(17) and Naughton et al.(87)

Most included studies assessed the risk of CVD associated with any motor vehicle crash in which the involved individual was a driver. However, some heterogeneity in the definition of a crash exists between the studies. Vernon et al.(76) and McGwin et al.(77) analyzed crash data for individuals who were deemed to be "at fault" in the crash, while Koepsell et al.(86) and Ysander focused their attention on the risk for an injurious motor vehicle crash.

Crash data from which crash rates were determined were obtained from two primary sources: databases and questionnaires. In order for data from databases to be informative, relevant information contained within it must be precise. Since we have no way of determining the precision of the information contained within any of the databases used to inform the studies included in this report, the degree of confidence that one may have in data extracted from these databases is not clear. The degree of confidence that one can have in crash rates derived from questionnaires is also unclear, primarily because questionnaires depend on reliable reporting by the individual being questioned.

Quality of Evidence Base

The findings of our assessment of the quality of the studies that comprise the evidence base for Key Question 1 are summarized in Table 21. Complete details of our quality assessment can be found in the study summary tables presented in Appendix G. Our assessment found that the quality of the included studies was not high. Four of the 15 included studies were graded as being moderate quality. The remaining 11 studies were graded as being low quality.

Table 21. Quality of that Assess Key Question 1

Reference	Year	Quality Scale Used	Quality Score	Quality
Vernon et al.(76)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.8	Moderate
Jovanovic et al.(79)	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	4.6	Low
McGwin et al.(77)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low

Reference	Year	Quality Scale Used	Quality Score	Quality
Guibert et al.(82)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
Dionne et al.(17)	1995	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	8.7	Moderate
Medgyesi et al.(16)	1995	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
Gresset and Meyer(85)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
Koepsell et al.(86)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	8	Moderate
Naughton et al.(87)	1982	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
Davies et al.(88)	1973	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	5.8	Low
Crancer and O'Neall(90)	1970	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
McMurray and Crancer(91)	1968	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	8	Moderate
Waller(92)	1967	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.7	Low
Ysander(93)	1966	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.1	Low
Waller(94)	1965	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Controlled Studies	7.1	Low

Generalizability of Evidence to Target Population

Important characteristics of the individuals represented in the 15 studies that comprise the evidence base for Key Question 1 are presented in Table 22. The information presented in this table demonstrates that currently available data that is directly generalizable to CMV drivers is extremely limited. Only two included studies included distinct populations of CMV drivers.(16,17) The remainder of the studies included private motor vehicle license holders, an unknown number of whom may have held commercial driver licenses.

The generalizability of the findings of these latter studies to CMV drivers is unclear. Exposure to risk is far lower among noncommercial vehicle drivers, women tend to be overrepresented, and the number of comorbidities suffered by included individuals will tend to be lower than that observed in CMV driver populations.

Several different types of CVD were represented in the included studies. The exact composition of CVD in each study was not always clear as study investigators

often simply reported that they included individuals with a CVD. However, in cases where such information was presented, it is clear that the patient populations within studies were heterogeneous. In some instances, study authors evaluated crash risk within the study group as a whole and also within different subgroups of individuals with a specific CVD. When such data were available, we extracted them with the aim of determining crash risk among subpopulations of individuals with specific forms of CVD.

Table 22. Individuals with CVD Enrolled in Studies that Address Key Question 1

Reference	Year	Type of CVD (%)	Mean Age (SD)	% Male	% CMV Drivers	Number with Restricted Drivers License Due to CVD	Generalizability to CMV Drivers
Vernon et al.(76)	2002	All CVD, including heart disease, rhythm disturbances, history of myocardial infarctions, heart surgery, or hypertension (% NR*)	55.8 (19.4)	NR	NR	41 (of 19,939) with restricted licensure for that reason	Unclear
Jovanovic et al.(79)	1999	Hypertension (52.9%) Arrhythmia (28.4%) Coronary artery disease (10.9%) Thromboangiitis obliterans (7.7%)	51.8 (12.3) cases, 52.1 (11.9) controls	69.2% of cases, 70.7% of controls	39.6% of cases and 29.3% of controls were not amateur drivers	NR	Unclear
McGwin et al.(77)	2000	NR	NR	NR	0%	NR	Unclear
Guibert et al.(82)	1998	56.1% coronary heart disease; other types not reported	NR	100%	NR	NR	Unclear
Dionne et al.(17)	1995	NR	NR	100%	100%	NR	Good
Medgyesi et al.(16)	1995	Ischemic heart disease (NR) Pulmonary circulation disease (NR) Conduction disorders (NR) Cardiac arrhythmias (NR) Heart failure (NR)	NR	NR	Subgroup of individuals with commercial license	"Program" drivers (n = 906)	Subgroup - Good
Gresset and Meyer(85)	1994	Ischemic heart disease (18.6%), Arrhythmias (2.1%), Heart failure (1.3%), Hypertension (12.6%); all CVD combined 32% of all cases	NR	100%	0%	NR	Unclear

Reference	Year	Type of CVD (%)	Mean Age (SD)	% Male	% CMV Drivers	Number with Restricted Drivers License Due to CVD	Generalizability to CMV Drivers
Koepsell et al. 1992(86)	1992	Myocardial infarction (7.3%), Angina pectoris (19.7%), Coronary-artery bypass graft (2.6%), atrial fibrillation (5.6%), paroxysmal supraventricular tachycardia (3.4%), premature ventricular contractions (8.5%), sinus bradycardia (14.6%), first-degree AV block (5.1%), second or third-degree AV block (0.4%), left bundle branch block (1.3%), right bundle branch block (2.6%), left anterior hemiblock (2.6%), pacemaker (1.7%), hypertension (33.3%)	NR	50%	NR	NR	Unclear
Naughton et al.(87)	1982	Acute myocardial infarction (past) (42.8%), Angina pectoris or other acute ischemic heart disease (30.2%), acute congestive failure, conduction defect or arrhythmia secondary to ischemic heart disease (13.4%), chronic ischemic heart disease (13.5%)	NR	76%	NR	NR	Unclear
Davies et al.(88)	1973	NR	NR	68.9%	NR	318	Unclear
Crancer and O'Neall(90)	1970	Arteriosclerosis (30%), hypertension (24.9%), rheumatic (17.9%), other heart disease (27.4%)	Median age 60	NR	NR	474 (100%)	Unclear
McMurray and Crancer(91)	1968	NR	NR	NR	NR	NR	Unclear
Waller(92)	1967	NR	70.5 (variance)	47%	NR	NR	Unclear
Ysander(93)	1966	Valvular heart disease (NR) Coronary heart disease (NR) Other heart disease (NR) Hypertension (NR)	Age Range. 18 to 60 years; mean NR	81%	NR	NR	Unclear
Waller(94)	1965	Cardiac disease (18% of total records, 45% of those with CVD); hypertension (5.5% of total records	Of CVD cases, 52; of controls 41	85.2% of CVD cases, 55% of controls	NR	NR	Unclear

CVD Cardiovascular disease.
CMV Commercial motor vehicle.
NR Not reported.
SD Standard deviation.

Findings

The findings of each of the 15 studies that address Key Question 1 are presented in detail in Appendix G. As stated above, only two of these 15 studies enrolled a population of individuals comprised of CMV drivers. One of these studies was designed specifically to examine the effects of CVD on crash risk among CMV

drivers.(17) The other study stratified drivers by driver license endorsement class so that relevant data on crash risk pertaining specifically to CMV drivers could be extracted.

As stated previously, the evidence base for Key Question 1 is comprised of two distinct types of case-control studies. Thirteen studies compared crash risk among individuals with CVD (cases) and a comparable group of individuals who did not have the disorder (controls). Four studies compared the prevalence of CVD among individuals who had been involved in a crash (cases) and a comparable group of individuals who had not (controls). Although both types of study may be considered to address the same question from a qualitative perspective ("Does CVD represent an increased crash risk?"), they differ significantly from a quantitative perspective. Outcome data from the former set of studies were presented as an RR[7]. Outcome data from the latter group of studies were presented as the OR[8].

Studies of CVD and Crash Risk among CMV Drivers

Two studies presented data directly relevant to the question of whether CVD has an impact on CMV driver safety.(16,17) Because of the direct relevance of data from these studies to CMV drivers, we discuss the findings of these studies separately from the remainder of the studies that comprise the evidence base for Key Question 1.

Study of Medgyesi and Colleagues

Medgyesi et al.(16) (Quality Score: 7.7; Quality Rating: Minimally acceptable) compared crash risk among drivers with CVD (any type) and matched (age, sex, residence, license class, and driving period[9]) controls. The study investigators stratified all drivers by driver license class. In Saskatchewan, where the study took place, five driving license endorsement classes exist (Table 23).

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[7] The incidence of crash among individuals with CVD divided by the incidence of crash among comparable individuals who do not have CVD.

[8] The odds of an individual who crashed having CVD divided by the odds of an individual who did not crash having CVD.

[9] The amount of driving could not be controlled for; only the driving period

Table 23. Driver License Endorsement Classes in Saskatchewan, Canada

Endorsement	Type(s) of Vehicle	Relevant to U.S CMV License
Class 1	Power units and semi-trailers	Yes
Class 2	Buses with a seating capacity in excess of 24 passengers	Yes
Class 3	Trucks with more than two axles	Yes (?)
Class 4	Buses with a seating capacity of 24 or less	Yes (?)
Class 5	Cars, vans, and two-axle trucks	No

Madgyesi et al. presented crash data for drivers with Class 1 through 4 licenses separately from Class 5 drivers. While Class 1 and Class 2 license holders are directly comparable to CMV drivers in the United States, it is unclear to what extent this is the case with Class 3 and Class 4 license holders. Regardless, we considered Madgyesi's findings for all four classes of license. Unfortunately, we are precluded from calculating an estimate of the risk ratio for this study. This is largely due to the fact that crash data for controls who had Class 1 through Class 4 licenses were not presented; only crash data for the entire control group (Class 1 through Class 5) were presented. This control group was dominated by data from Class 5 drivers. Consequently, evidence on the relationship between CVD and crash risk is limited to the findings of the single study executed by Dionne et al.(17)

Study of Dionne and Colleagues

Dionne et al.(17) estimated the effects of different medical conditions on truck driver crash risk using data from a nested case-control study (Quality Score: 8.7; Moderate). The data analyzed by Dionne et al. were part of the large anonymous file originally created by Laberge-Nadeau and colleagues. The anonymous file was created by merging data from five separate data files from the Societe de l'assurance automobile du Quebec on permits, crashes, violations, demerit points, and health status (medical conditions) to comprise a database detailing information on 20,208 permit holders in Quebec, Canada. The file on health status contained the permit holders who were required by regulation to undergo a medical or ophthalmologic examination. Also linked to this file were the results of a telephone survey of exposure and driving habits that was performed in 1990.

For this study Dionne et al. focused their analysis on data from male drivers who drove a truck at work. Of the 6,190 individuals listed in the database with a CMV license (a Class 1 or 3 license), 3,960 individuals responded to a survey pertaining to

their current driving status. Of these individuals, 1,307 reported operating a truck at work at the time of the survey.

Dionne collected data on a number of variables, including the following:

- The total number of truck crashes for the four year period of 1987 through 1990
- The age of each driver
- Each driver's permit class
- Details on the existence of several medical conditions (categories included good health, CHD, hypertension, problems of binocular vision, diabetes, and a no evaluation category)
- Whether each driver was the owner of the truck he drove at work
- The observation period (with 1990 as the reference period)
- The distance driven by each driver at work
- The number of hours each driver spent behind the wheel
- Whether each driver pulled a trailer at work
- Whether the driver typically drove after 8 p.m.
- The working radius for each driver
- The type of road typically driven on

For each driver, Dionne et al. modeled (using negative binomial regression models), the number of crashes in a year as a function of the variables listed above. In all, Dionne et al. developed six models. From a safety analyst's standpoint, Dionne's Model 6 is the most informative since it comprises the best fit and the largest number of significant variables.

The findings of this model are summarized in Table 24. Note that a negative coefficient indicates that crash risk is reduced, and a positive coefficient indicates that crash risk is increased. Dionne's analysis demonstrated that neither CAD nor hypertension were significant risk factors for crash in CMV drivers.

Table 24. Findings of Dionne et al.

Explanatory Variable	Coefficient*	t statistic	Significant (P <0.05)?
Age Group			
≤25 years	Omitted	Omitted	
26-30 years	0.13	0.43	
31-35 years	-0.09	-0.29	
36-40 years	-0.49	-1.54	
41-45 years	-0.27	-0.89	
46-50 years	-0.60	-1.96	Yes
51-55 years	-0.48	-1.54	
56-60 years	-0.33	-0.98	
>60 years	-0.14	-0.34	
Class 1 Drivers			
Medical Condition			
Coronary disease	0.16	0.73	
Hypertension	-0.36	-1.45	
Truck Owner	-0.05	-0.26	
Distance Driven			
≤15,000 km/year	Omitted	Omitted	
15,001 to 40,000 km/year	0.57	2.37	Yes
40,001 to 87,500 km/year	0.90	3.57	Yes
>87,500 km/year	1.08	3.97	Yes
Pull a Trailer	0.03	0.19	
Drive after 8 p.m.	-0.26	-1.48	
Working Radius			
<50 km	Omitted	Omitted	
50 to 160 km	0.58	2.90	Yes
>160 km	0.34	1.38	
Type of Road			
Highway	-0.50	-1.94	Yes
Country road	-0.38	-1.55	
City street	Omitted	Omitted	
Highways + country roads	-0.04	-0.10	
City streets + country roads	-0.29	-0.90	
City streets + highways	0.02	0.07	
Number of Hours			
≤720	Omitted	Omitted	
721 to 1,200	0.24	0.99	
1,201 to 1,728	0.62	2.72	Yes
>1,728	0.49	2.07	Yes
Other Class License			
Medical Condition			
Coronary disease	-0.36	-0.55	
Hypertension	0.29	0.79	
Truck Owner	-0.78	-2.40	Yes
Distance Driven			
≤10,000 km/year			
10,001 to 22,500 km/year	0.30	1.45	

Explanatory Variable	Coefficient*	t statistic	Significant (P <0.05)?
22,501 to 40,000 km/year	0.21	1.50	
>40,000 km/year	0.74	1.81	Yes
Pull a Trailer	0.13	0.37	
Drive after 8 p.m.	-0.65	-1.92	Yes
Working Radius			
<50 km	-0.13	-0.32	
50 to 160 km	-0.30	-0.76	
>160 km	Omitted	Omitted	
Type of Road			
Highway	0.03	0.06	
Country road	-0.17	-0.53	
City street	Omitted	Omitted	
Highways + country roads	0.10	0.22	
City streets + country roads	-0.42	-0.74	
City streets + highways	-0.01	-0.04	
Number of Hours			
≤585	Omitted	Omitted	
586 to 1,000	-0.00	-0.01	
1,001 to 1,500	0.22	1.63	
>1,500	1.05	2.61	Yes

*A negative coefficient indicates that crash risk is reduced and a positive coefficient indicates that crash risk is increased.

Studies of Effect of CVD on Crash Risk in General Driver Population

Fourteen included studies provided data pertaining to the influence of CVD on the safety of the general driver population.[10] As noted above, crash risk was assessed using two different approaches. The first approach compared the prevalence of CVD among a group of individuals who had experienced a motor vehicle crash with that observed among a group of individuals who had not experienced such a crash. The measure of the difference in crash risk measured by this type of study is usually the OR (the odds of having CVD having experienced a motor vehicle crash divided by the odds of having CVD having not experienced a crash). For ease of communication, we henceforth refer to these studies as "OR studies."

The second approach to determining the risk associated with CVD and driver safety is to compare the incidence rate of motor vehicle crashes that occur among individuals who have CVD with the crash rate among comparable individuals who do not have the disorder. The measure of the difference in crash

[10] 13 studies plus a subset of individuals included in the study of Medgyesi et al.(16)

risk reported by this type of study is usually the RR (the ratio of crash incidence observed among individuals with CVD and comparable individuals who do not have the disorder). Henceforth, we refer to these studies as "RR studies."

CVD and Crash Risk: Findings of Crash RR Studies

Ten included studies reported on the ratio of the incidence of crashes occurring among populations of individuals with CVD and the ratio of the incidence of crashes occurring among individuals without the disorder.(16,76,79,87,88,90-94) The findings of these studies are presented in Table 25.

Table 25. Findings of Crash RR Studies

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			Crash Rate (cases)	Crash Rate (controls)	Rate Ratio* (95% CI)	*P* =*	
CVD (Nonspecific) and Crash Risk							
Vernon et al.(76)	2002	Crashes per 10,000 license days	1.35	0.98	1.37 (0.43–4.38)	0.595	No
Jovanovic et al.(79)	1999	% who crashed over 5-year period	22.4	10.3	2.18 (1.04–4.55)	0.038	Yes
Medgyesi et al.(16)	1995	Crashes per 1,000 drivers	33	55	1.67 (1.08–2.57)	0.020	Yes
Davies et al.(88)	1973	Crashes per 100 drivers	9.10	7.10	1.28 (0.48–3.42)	0.622	No
McMurray and Crancer(91)	1968	Crashes per 100 drivers	25.87	25.28	1.02 (0.60–1.77)	0.943	No
Waller(92)	1967	Crashes per 1,000,000 miles	14.7	9.1	1.22 (0.71–3.69)	0.257	No
Ysander(93)	1966	Crashes per 100 drivers disease	1.7	7.7	0.22 (0.04–1.16)	0.078	No
Waller(94)	1965	Crashes per 1,000,000 miles	14.6	9.0	1.62 (0.71–3.72)	0.254	No
Hypertension and Crash Risk							
Jovanovic et al.(79)	1999	% who crashed over 5-year period	28.1	10.3	2.73 (1.33–5.57)	0.006	Yes
Crancer and O'Neall(90)	1970	% of drivers who crashed	23.7	12.5	1.90 (0.96–3.76)	0.065	No
Arrhythmia and Crash Risk							
Jovanovic et al.(79)	1999	% who crashed over 5-year period	11.4	10.3	1.11 (0.48–2.57)	0.807	No
CAD and Crash Risk							
Jovanovic et al.(79)	1999	% who crashed over 5-year period	14.7	10.3	1.43 (0.64–3.17)	0.381	No

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			Crash Rate (cases)	Crash Rate (controls)	Rate Ratio* (95% CI)	*P* =*	
Crancer and O'Neall(90)	1970	Crashes per 100 drivers	29.1	14.8	1.97 (1.05–3.69)	0.034	Yes
Naughton et al.(87)	1982	% crashed per year	28	33.6	0.83 (0.51–1.38)	0.463	No
Other CVD							
Jovanovic et al.(79)	1999	Crashes over 5-year period (Thromboangiitis obliterans)	35.1	10.3	3.44 (1.71–6.88)		Yes
Crancer and O'Neall(90)	1970	(Rheumatic heart disease)	18.2	18.2	1.00 (0.52–1.92)		No
Crancer and O'Neall(90)	1970	(Other heart disease)	21.5	13.4	1.60 (0.81–3.17)		No

* Calculated by ECRI; estimates of confidence intervals based on transformation of available data to crashes/person-year. Effect size estimates >1.0 indicate that diabetics are at increased risk for a motor vehicle crash than comparison group; †Authors presented findings of six separate models. The coefficients associated with these models are presented in Appendix E in the study summary tables for Dionne et al; ‡Authors argue that it was not necessary (found no evidence that exposure had an impact on crash rate)

§ Based on population data from Department of Transportation.

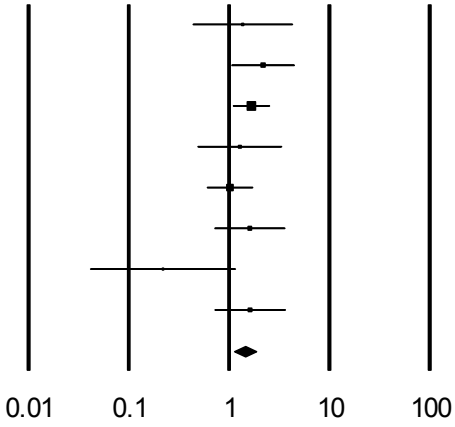
CI Confidence interval.
NC Not calculated.
NR Not reported.
NS Not statistically significant.
OR Odds ratio.
RD Rate difference.
RR Risk ratio.

CVD and Crash Risk (RR Studies)

Eight included studies (Median Quality Score: 7.7; Quality Rating: Low) provided data on the relative incidence of crash among individuals who have CVD (any type) and comparable individuals without the disorder.(16,76,79,88,91-94) The findings of the eight studies were quantitatively consistent (homogeneity tests: Q = 8.26; *P* = 0.314: I^2 = 14.802). Consequently, we pooled the data from the eight studies with the aim of calculating a summary crash RR estimate (Figure 3).

Figure 3. Crash Risk among Individuals with CVD (any type) Compared to Controls

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.370	0.429	4.372	0.532	0.595
Jovanovic	2.180	1.042	4.560	2.070	0.038
Medgyesi	1.670	1.084	2.574	2.324	0.020
Davies	1.280	0.480	3.417	0.493	0.622
Crancer and McMurray	1.020	0.594	1.752	0.072	0.943
Waller (1968)	1.610	0.706	3.670	1.133	0.257
Ysander	0.220	0.041	1.185	-1.763	0.078
Waller (1965)	1.620	0.708	3.708	1.142	0.254
	1.430	1.111	1.841	2.773	0.006



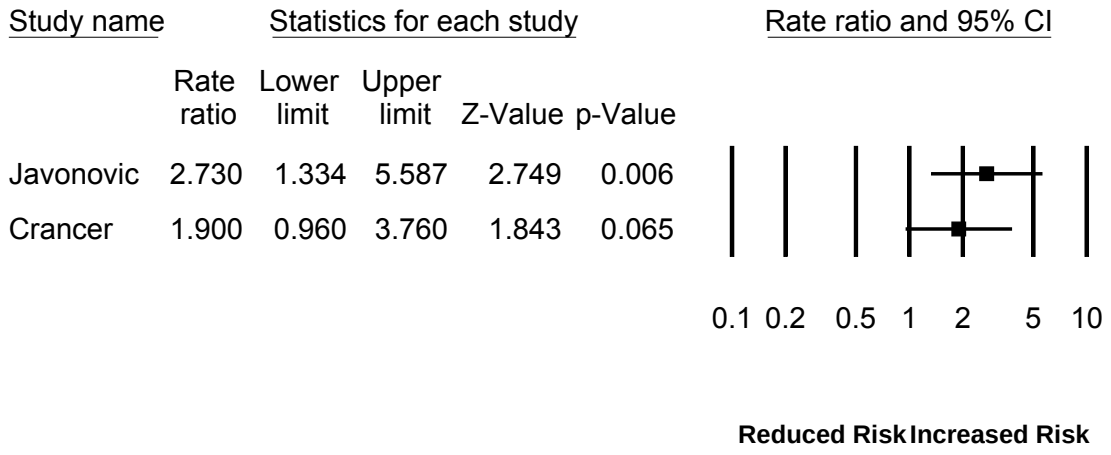
The results of this analysis provide support, albeit minimally acceptable, for the contention that individuals with CVD are at an increased risk for a motor vehicle crash when compared to comparable individuals without CVD. Our analysis suggests that the crash RR associated with CVD is 1.43 (95% CI: 1.11 to 1.84). Put another way, the risk for a motor vehicle crash among individuals with characteristics similar to the individuals included in the evidence base above is approximately 43% greater than comparable individuals without CVD. Thus, if the underlying crash risk for a CMV driver is 0.08 crashes per person-year, the crash risk for a CMV driver with CVD will be approximately 0.11 crashes per person-year.

Although a series of sensitivity analyses (Appendix H) found that the estimate above was robust, the strength of our conclusion must be tempered by the fact that the studies providing the data used to produce this estimate were of low methodologic quality. In addition, the fact that the crash data used in our analyses did not pertain to CMV drivers may further limit the value of our findings, because the generalizability of our findings to this population of drivers is unknown.

Hypertension and Crash Risk (RR Studies)

Two included studies (Median Quality Score: 6.2; Quality Rating: Low) reported on the difference in the incidence of a motor vehicle crash observed among individuals with hypertension[11] and comparable individuals without the disorder.(79,90) The findings of these studies are summarized in Table 25 and are represented graphically in Figure 4 below.

Figure 4. Hypertension and Relative Crash Risk



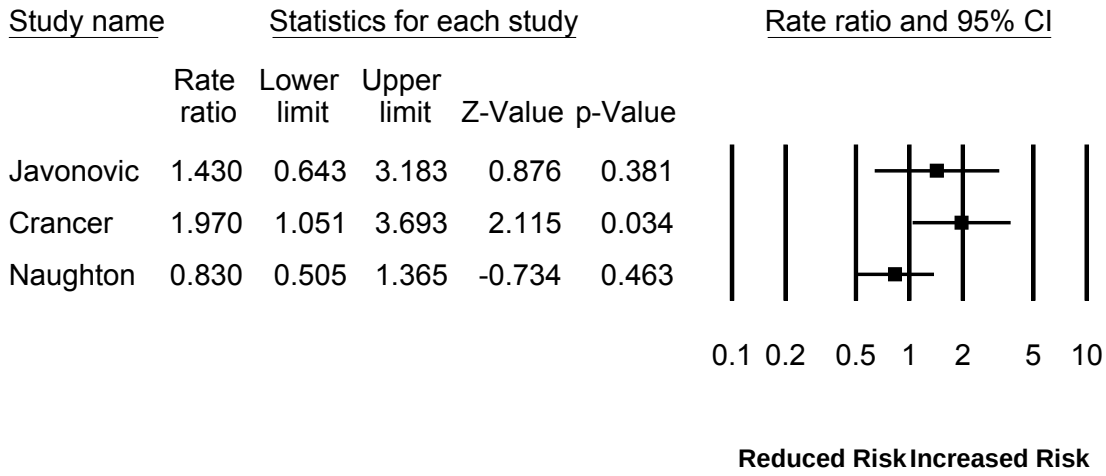
The findings of both studies suggest that individuals with hypertension are at an increased risk for a motor vehicle crash when compared to individuals without CVD. Because data from only two studies are available, we have not pooled their data in order to obtain a summary estimate of the magnitude of this increased risk.

CAD and Crash Risk (RR Studies)

Three included studies (Median Quality Score: 7.7; Quality Rating: Low) reported on the difference in the incidence of a motor vehicle crash observed among individuals with CAD and comparable individuals without the disorder.(79,87,90) The findings of these studies are summarized in Table 25 and are represented graphically in Figure 5.

[11] Defined by Jovanovic as a systolic BP of >18.7 kPa and a diastolic BP of >12 kPa. Not defined by Crancer.

Figure 5. CAD and Crash Risk

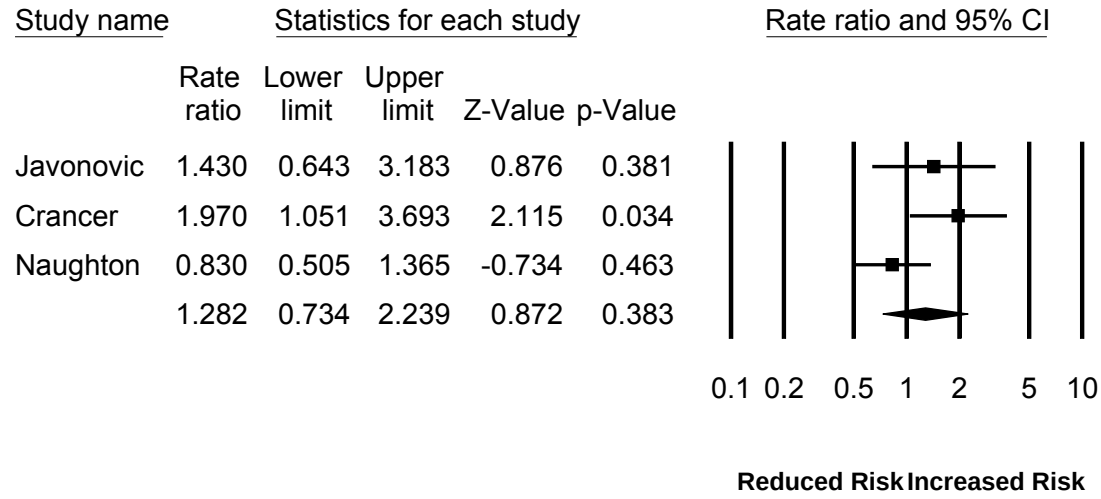


One of the three studies found that individuals with CVD are at an increased risk for a crash.(90) The remaining two studies, however, did not make this observation.(79,87) A test of homogeneity found that the findings of the three studies were heterogeneous (Q = 4.682, *P* = 0.096; I^2 = 57.279). Consequently, we did not pool the data from the three studies using a fixed-effects meta-analysis, nor did we attempt to explore this heterogeneity using meta-regression[12].

Pooling of these data using a random-effects meta-analysis (Figure 6) found that individuals with CAD demonstrate a tendency for experiencing more crashes than their counterparts who do not have CAD (RR = 1.282, 95% CI: 0.734 to 2.239). Because the confidence intervals encompass an RR of one, however, we cannot discern whether this tendency in the data is meaningful. We thus refrain from drawing an evidence-based conclusion pertaining to the crash risk associated with CAD at this time.

[12] ECRI requires at least 10 studies for meta-regression or subgroup analysis to be attempted.

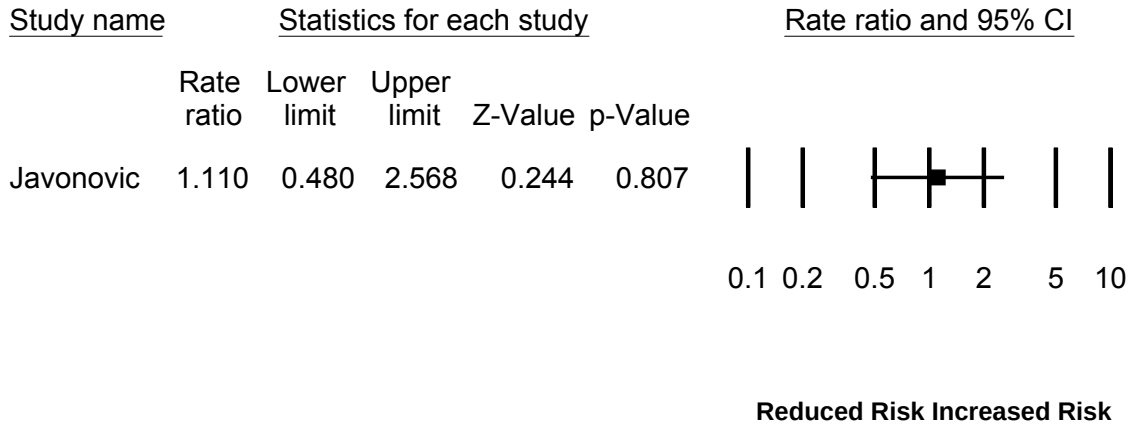
Figure 6. CAD and Crash Risk (Random-effects Meta-analysis)



Arrhythmia and Crash Risk (RR Studies)

A single, low quality (Quality Score: 4.6) study compared the crash rates among individuals with an arrhythmia with crash rates among individuals without CVD. This study did not provide evidence in support of the contention that individuals with arrhythmias are at an increased risk for a motor vehicle crash (Figure 7). Because the data were obtained from a single small, low-quality study, we refrain from drawing an evidence-based conclusion at this time.

Figure 7. Arrhythmia and Crash Risk



Findings of studies that compared the prevalence of CVD among drivers who did and did not crash

Four of the 14 studies that assessed the crash risk associated with CVD among the general driver population were OR studies.(78,82,85,86) Relevant findings from these studies are summarized in Table 26.

Table 26. Findings of OR Studies

Reference	Year	Units	Crash Rate Data				Evidence of increased Crash Risk
			% with Disorder (crashers)	% with Disorder (non-crashers)	Effect Size (95% CI)	*P* =*	
CVD (non-specific) and Crash Risk							
McGwin et al.(78)	1999	% having disorder	26.0	20.2	OR = 1.5 (1.0–2.2)	0.044	Yes
Guibert et al.(82)	1998	% having disorder	NR	NR	OR = 0.82 (0.67–1.00)	0.052	No
Gresset and Meyer(85)	1994	% having disorder	32.0	31.1	OR = 1.04 (0.91–1.20)	0.578	No
Hypertension and Crash Risk							
McGwin et al.(78)	1999	% having disorder	42.9	45.7	OR = 0.90 (0.60–1.30)	0.592	No
Gresset and Meyer(85)	1994	% having disorder	12.6	13.1	OR = 0.95 (0.78–1.16)	0.612	No
Koepsell et al.(86)	1994	% having disorder	33.0	37.0	OR = 0.80 (0.60–1.07)†	0.131	No
Arrhythmia and Crash Risk							
Gresset and Meyer(85)	1994	% having disorder	2.1	1.3	OR = 1.53 (0.89–2.65)	0.127	Yes
Koepsell et al.(86)	1994	% having disorder	23.5	24.7	OR = 1.20 (0.85–1.70)†	0.303	No
CAD and Crash Risk							
Koepsell et al.(86)	1994	% having disorder	21.4	15.5	OR = 1.40 (1.10–1.78)†	<0.05	Yes
Other CVD and Crash Risk							
Gresset and Meyer(85)	1994	% having disorder	1.3	1.4	OR = 0.94 (0.53–1.66)	NS	No
Koepsell et al.(86)	1994	% having disorder	9.5	6.9	OR = 1.6 (0.9–2.8)	NS	No

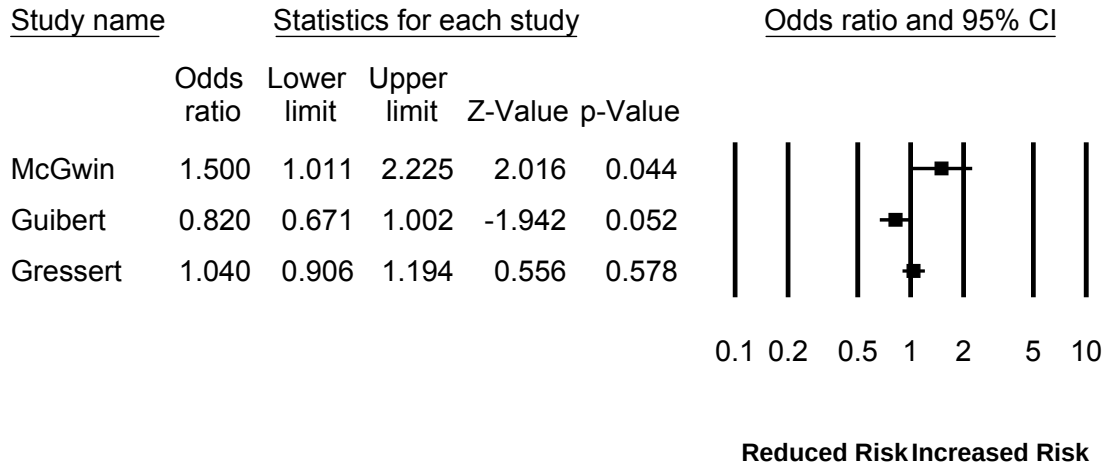
CAD Carotid artery disease.
CVD Cardiovascular disease.
NR Not reported.
NS Not significant.
OR Odds ratio.
* Calculated by ECRI from reported data; †Confidence intervals were not symmetrical when transformed to LN OR, consequently we recalculated confidence intervals using available data.

CVD and Crash Risk

Three studies (Median Quality Score: 7.7; Quality Rating: Low) presented data on the odds of an individual who experienced a crash having CVD relative to the

odds of having the disorder and not experiencing a crash. These data are summarized by the forest plot shown in Figure 8.

Figure 8. CVD and Crash Risk (OR Studies)

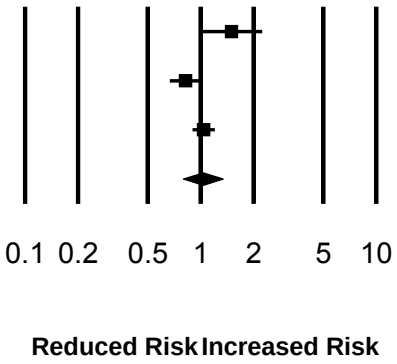


The forest plot suggests that the data from the three included studies are inconsistent. One of the three studies suggests that CVD increases crash risk,(78) one study suggests that CVD decreases crash risk,(82) and the third study finds no evidence of an increase or a decrease in crash risk.(85) Formal homogeneity testing found the data presented in Figure 8 to be heterogeneous ($Q = 8.12$; $P = 0.017$: $I^2 = 75.44$). Consequently, pooling these data using a fixed-effects meta-analysis (FEMA) was precluded. Because the evidence base consisted of <10 studies, we did not attempt to explain the observed heterogeneity using meta-regression or subgroup analysis.

In order to draw a qualitative conclusion we pooled the data from three available studies using a random-effects meta-analysis (Figure 9). The results of this latter analysis do not provide evidence to support the contention that, when considered as a homogeneous group, individuals with any type of CVD are overrepresented among individuals who have experienced a motor vehicle crash.

Figure 9. CVD and Crash Risk (OR studies-Random-effects Meta-analysis)

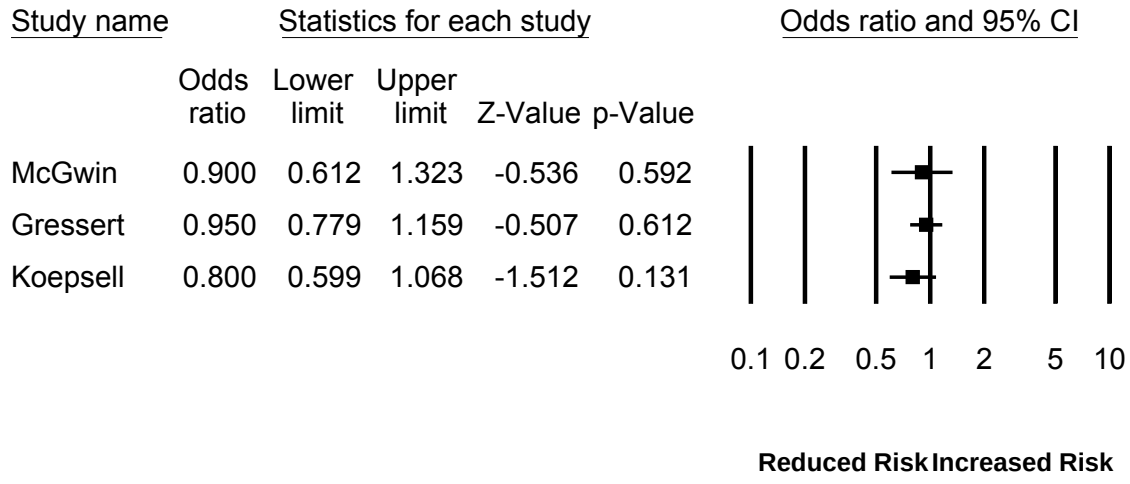
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
McGwin	1.500	1.011	2.225	2.016	0.044
Guibert	0.820	0.671	1.002	-1.942	0.052
Gressert	1.040	0.906	1.194	0.556	0.578
	1.035	0.800	1.340	0.261	0.794



Hypertension and Crash Risk

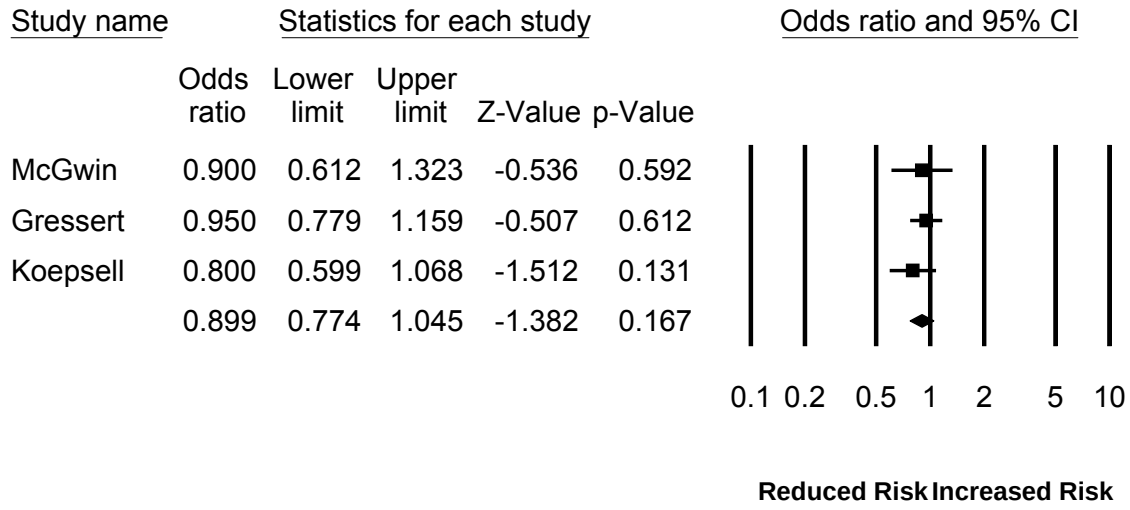
Three studies (Median Quality Score: 7.7; Quality Rating: Low) presented data on the odds of an individual who experienced a crash having hypertension relative to the odds of a comparable individual who did not experience a crash having the disorder.(78,85,86) These data are summarized by the forest plot shown in Figure 10. None of the three included studies provided support for the contention that individuals with hypertension are overrepresented in populations of individuals who have experienced a motor vehicle crash.

Figure 10. Hypertension and Crash Risk (OR Studies)



The findings of the three studies were found to be quantitatively consistent (homogeneity tests: Q = 0.922; *P* = 0.631: I^2 = 0.000). Consequently, we pooled the data from the three studies with the aim of calculating a summary OR estimate. Unlike the findings of our previous analysis of data from two RR studies that compared crash rates among individuals with hypertension and comparable individuals without the disorder, the results of this analysis (Figure 11) do not provide support for the contention that individuals with hypertension are at an increased risk for a motor vehicle crash and are therefore overrepresented among cohorts of individuals who have experienced one. More data will be required before an evidence-based conclusion pertaining to the crash risk associated with hypertension can be drawn.

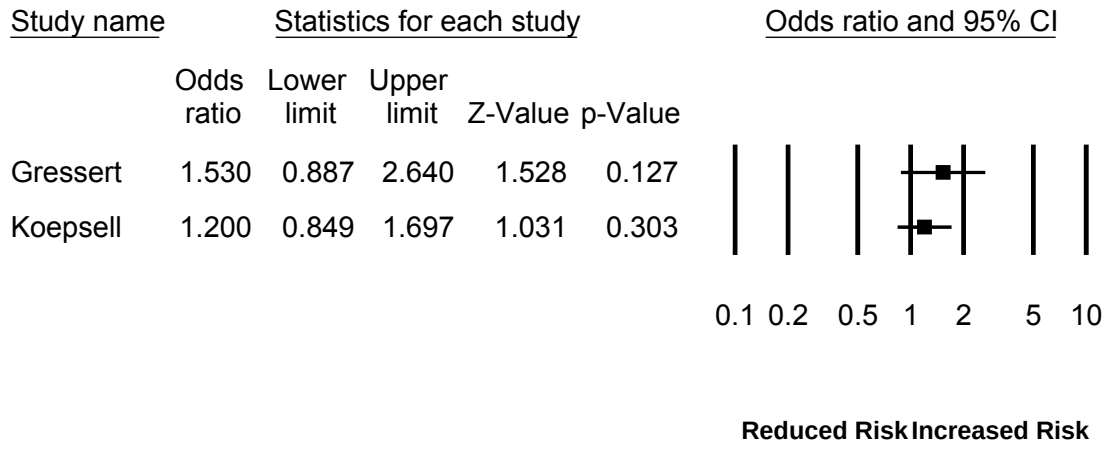
Figure 11. Fixed-effects Meta-analysis of Hypertension and Crash-Risk Data (OR Studies)



Arrhythmia and Crash Risk

Two studies (Median Quality Score: 7.7; Quality Rating: Low) presented data on the odds of an individual who experienced a crash having arrhythmia relative to the odds of a comparable individual who did not crash having the disorder (Figure 12).(85,86) Because data from only two relevant studies were available and they were of low quality, we have not pooled the relevant data from these studies using meta-analysis.

Figure 12. Arrhythmia and Crash Risk (OR Studies)

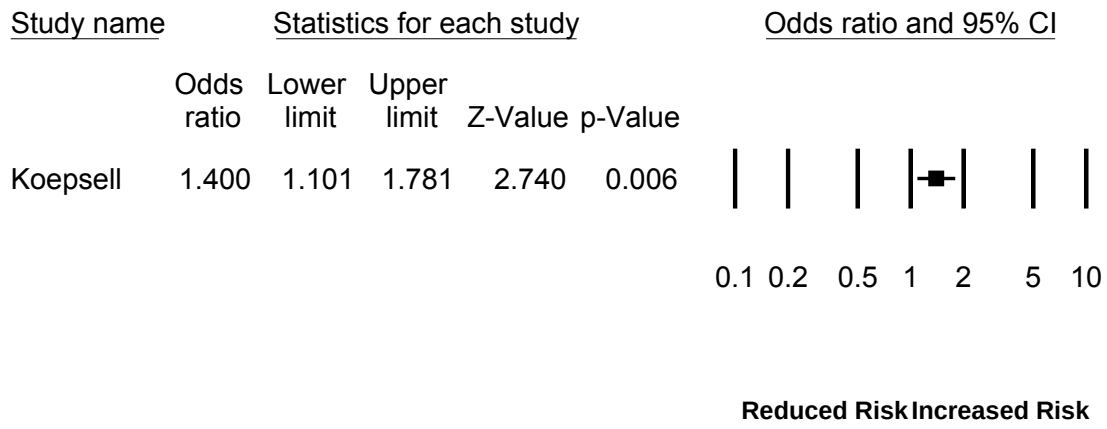


Both included studies were inconclusive. Neither study provided support for the contention that individuals with arrhythmia are at an increased risk for a motor vehicle crash and are therefore overrepresented among cohorts of individuals who have experienced one. Although both included trials independently demonstrate a trend in the data suggesting that individuals with hypertension may be at increased risk for a crash, the studies were too small to conclusively demonstrate such an effect. Consequently, we refrain from drawing an evidence-based conclusion at this time.

CAD and Crash Risk (OR Studies)

A single moderate-quality study (Quality Score: 8.0) presented data on the odds of an individual who experienced a crash having CAD relative to the odds of an individual who did not crash having the disorder (Figure 13).(86)

Figure 13. CAD and Crash Risk (OR Studies)



Data from Koepsell et al.(86) suggest that individuals with CAD are at an increased risk for a motor vehicle crash (OR = 1.40, 95% CI: 1.10 to 1.78; P = 0.006). However, data from a single low-quality study is not sufficient to warrant the production of an evidence-based conclusion.

Section Summary

A number of conclusions can be drawn from the findings of the analyses described above. These conclusions are presented below:

Drivers of CMVs

1. **A paucity of data from studies that enrolled CMV drivers with CVD precludes one from determining whether CMV drivers with the disorder are at an increased risk for a crash.**

   Two studies presented data directly relevant to the question of whether CVD has an impact on CMV driver safety.(16,17) Medgyesi et al.(16) (Quality Rating: Minimally acceptable) presented crash data for drivers with Class 1 through 4 licenses (comparable to U.S. CMV drivers) separately from Class 5 license holders (private motor vehicle drivers). However, we were precluded from calculating an estimate of the risk ratio for this study, because crash data for the controls with Class 1 through Class 4 licenses were not presented. Only crash data for the entire control group (Class 1 through Class 5) were presented, and this group was dominated by Class 4 license holders. Thus, useful evidence on the relationship between CVD and crash risk among CMV drivers is limited to the findings of just one study.

   Dionne et al.(17) estimated the effects of different medical conditions on truck-driver crash risk using data from a nested case-control study (Quality Rating: Moderate). These investigators did not find evidence supporting the contention that CMV drivers with CVD are at an increased risk for a crash. While these results are interesting, the study is not high quality and its results have not been replicated. Consequently, an evidence-based conclusion pertaining to whether CMV drivers with diabetes are at an increased risk for a motor vehicle crash is not drawn at this time.

Drivers of Non-CMVs

Because data from studies of CMV drivers with CVD are scarce, we deemed it worthwhile to examine relevant data from studies that investigated crash risk associated with CVD among more general driver populations. While the generalizability of these studies' findings to CMV drivers may not be clear, such findings do at the very least allow one the opportunity to draw evidence-based conclusions about the relationship between CVD and motor vehicle crash risk in general.

The findings of our analyses of crash data from these studies is summarized in Table 27.

Table 27. Summary of Findings

CVD	RR studies	Strength of Evidence Stability of SES	OR studies	Strength of Evidence Stability of SES
Any	Increased crash risk RR = 1.43 (95% CI: 1.11–1.84)	Strength of Evidence: Acceptable Stability of Estimate: Low	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable
Hypertension	Increased crash risk RR = NP	Strength of Evidence: Acceptable Stability of Estimate: Unstable	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable
Arrhythmia	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable
CAD	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable
Other	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable	No evidence-based conclusion	Strength of Evidence: Unacceptable Stability of Estimate: Unstable

NP Not presented.
OR Odds ratio.
RR Rate ratio.
SES Summary effect size (summary estimate of RR).

The conclusions that we draw from the findings summarized above are as follows:

4. **As a group, drivers with CVD are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Minimally acceptable).**

   - **The magnitude of this increased risk is small but statistically significant (RR = 1.45, 95% CI: 1.11–1.84). In other words, the crash risk for an individual with CVD is 1.43 times greater than a comparable individual who does not have the condition (Stability of Estimate: Acceptable).**

   Eight studies (Quality Rating: Low) presented data on the relative incidence of crash among individuals who have CVD (any type) and comparable individuals without the disorder. The findings of the eight studies were quantitatively consistent. Pooling of the data that the crash-rate ratio associated with CVD is 1.43 (95% CI: 1.11 to 1.84). Thus, if the underlying crash risk for a CMV driver is 0.08 crashes per person-year, the crash risk for a CMV driver with CVD will be approximately 0.11 crashes per person-year. Although a

series of sensitivity analyses found this estimate to be robust, the strength of our conclusion must be tempered by the fact that the studies providing the data used to produce this estimate were of low methodologic quality. In addition, the fact that the crash data used in our analyses did not pertain to CMV drivers may further limit the value of our findings. This is because the generalizability of our findings to this population of drivers is unknown.

5. **Drivers with hypertension are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Acceptable).**

    - **The magnitude of this increased risk cannot be determined at the present time.**

    Two included studies (Quality Rating: Low) reported on the difference in the incidence of a motor vehicle crash observed among individuals with hypertension and comparable individuals without the disorder. Because data from only two studies are available, we have not pooled their data in order to obtain a summary estimate of the magnitude of this increased risk. However, the findings of both studies suggest that individuals with hypertension are at an increased risk for a motor vehicle crash when compared to individuals without CVD.

6. **A paucity of consistent data precludes one from drawing evidence-based conclusions as to whether individuals with CAD, arrhythmias, or other types of CVD are at increased risk for a motor vehicle crash.**

Key Question 2: What are the risk factors for rupture of an aortic (abdominal or thoracic) aneurysm?

The aorta is the primary blood vessel in the body that provides the blood supply for most organs. It projects upward from the top of the left ventricle of the heart (ascending thoracic aorta), curves downward (the aortic arch), and travels through the chest (descending thoracic aorta) and into the abdomen (the abdominal aorta).When sections of the aorta become dilated, the tension on the

walls of the aorta intensifies (La Place's Law[13]) and the blood vessels become increasingly weak. This occurrence leads to an aneurysm and the possibility of aortic dissection, rupture, and death.(95,96) This aneurysm (an abnormal bulge or widening of part of the blood vessel wall greater than 50% of the normal vessel diameter) can form in any artery in the body, with most occurring in the brain and ascending and descending thoracic aorta and abdominal aorta.

In this section we review the evidence pertaining to rupture risk associated with two aortic aneurysms: those that occur in the abdominal aorta and those that occur in the thoracic aorta. The purpose of this review is to attempt to determine whether any risk factor or combination of risk factors can be used to determine the likelihood that an individual with a known aneurysm will experience rupture in the near future (1 to 2 years).

AAAs and Risk Factors for Rupture

Background

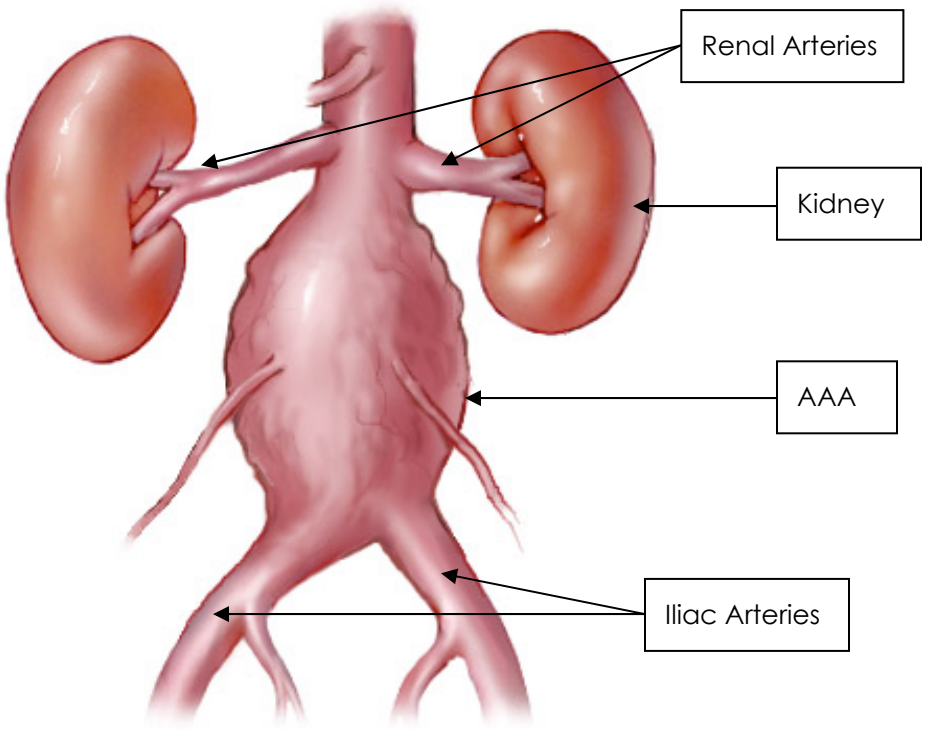
As their name suggests, AAAs occur in the section of the aorta that passes through the abdomen. More specifically, AAAs occur in the infrarenal segment of the abdominal aorta between the renal arteries and the iliac bifurcation. An aneurysm begins as a balloon-like enlargement in the wall of a weak or damaged artery. The pressure of blood passing through this weakened part of a blood vessel eventually forces the localized enlargement to expand outward (Figure 14).

The point at which a localized enlargement of the abdominal aorta becomes an aneurysm is not entirely clear, and several definitions exist in the literature. The four most common definitions of an AAA are as follows:

[13] Recently, Li and Kleinstreuer(332) suggested an alternative to La Place's Law for wall stress related to aneurysm rupture with the idea that their new formula would be able to compute aneurysm wall stress based on routine pressure and geometric measurements. This would allow for possible rupture prediction, while reducing the potential for overestimation or underestimation of actual aneurysm wall stress it is claimed, exists when La Place's law is applied. Another recent article from Di Martino et al.(401) also called the utility of La Place's law into question. These authors argued that the biomechanics which must be satisfied for La Place's law to function (simple geometry, small wall thickness to diameter ratio [less than 1/10th diameter], linear elastic homogenous material and static pressure load) do not exist in the human aorta, which is a more heterogenous environment.

1. The localized enlargement is equal to or greater than twice the normal vessel diameter.
2. The aortic diameter is at least 2.5 to 3.0 cm.[14]
3. The infrarenal aortic diameter is 1.5 times larger than the suprarenal aortic diameter.
4. The maximum diameter of the aorta is ≥4.0 cm, though this diameter can be exceeded between the mesenteric and renal arteries by ≥0.5 cm.

Figure 14. An Abdominal Aortic Aneurysm



Pathogenesis of AAAs

To date, no unified concept for the pathogenesis of AAAs has emerged. Weakening of the aortic wall due to degradation of collagen and elastin—the

[14] The normal diameter of the abdominal aorta is about 2.0 cm.

structural proteins found in the aortic extracellular matrix—may allow aneurysms to develop.(97) Although AAAs are often characterized as atherosclerotic (due to the involvement of the infrarenal abdominal aorta, which is most commonly affected by atherosclerotic processes), there is little support for the notion that this is the sole cause of AAA development. Recent observations have suggested that multiple factors contribute to their development, including genetic predisposition, acquired biochemical alterations in the structural matrix of the aortic wall, immunologic factors, and hemodynamic mechanical factors.(98,99) In addition, it has recently been suggested that elevated levels of inflammatory infiltrates in the aortic aneurysm wall, such as matrix metalloproteinases (which degrade collagen and elastin), plasminogen activators, serine elastoses, and cathepsins, may also contribute to the formation of an AAA.(100,101) Factors influencing the expansion of an AAA include initial diameter of the aneurysm, diastolic blood pressure, presence of renal failure, and location of the aneurysm (Table 28).(102)

Table 28. Factors Associated with AAA Expansion

Location of Aneurysm	Items Associated with Aneurysm
Abdominal Aorta	Genetic disorders of connective tissue: Marfan Syndrome Ehlers-Danlos Syndrome Turner's Syndrome Polycystic Kidney Disease
	Congenital Syndromes: Bicuspid aortic valve Coarctation of the aorta
	Atherosclerosis, including risk factors for this disease such as: • Age (≥55) • Male gender • Family history • Genetic factors • Hyperlipidemia • Hypertension • Smoking • Diabetes
	Giant Cell Arteritis: a disease that causes inflammation of the temporal arteries and other arteries in the head and neck, causing the arteries to narrow and blood flow to be reduced in the affected areas.
	Trauma
	Infectious Aortitis (due to diseases such as syphilis, salmonella, or staphylococcus)

Incidence and Prevalence

Approximately 4% of adults over age 65 harbor an AAA.(103) Over the last three decades, the population incidence of the condition has increased significantly. For example, the incidence of small aneurysms (<5 cm in diameter) has reportedly

increased tenfold, and the incidence of medium (5 to <7 cm in diameter) and large (≥7 cm in diameter) aneurysms has reportedly increased by a factor of between two and three.(103-107) This increase in the incidence of AAAs is generally attributed to an aging population combined with improvements in diagnostic imaging methods that enable the detection of smaller aneurysms.(108-114) Limited evidence, however, suggests that a genuine and persistent rise in the incidence of AAAs has occurred.(115,116)

The prevalence of AAAs in males over the age of 65 who have undergone ultrasound screening is ≈ 5%.(117) In a systematic review of risk factors for AAAs, Cornuz et al. found that the prevalence of AAAs ranged from 4.1% to 14.2% in males and from 0.35% to 6.2% in females.(118)

Signs and Symptoms

Approximately 75% of all AAAs are asymptomatic until rupture occurs. Depending on the lesion's diameter and position, some patients may present with symptoms such as back pain (retroperitoneal rupture), abdominal pain (intraperitoneal rupture), or a pulsating feeling in the abdomen (anterior/peritoneal cavity rupture) (Table 29). Symptoms associated with rupture include intense back and/or abdominal pain and signs of shock, such as shaking, dizziness, fainting, sweating, rapid heartbeat, and sudden weakness.

Table 29. Site of Abdominal Aortic Rupture (Darling et al. 1977)(119)

Aortic Site	Rupture (n = 102)
Anterior into Peritoneal Cavity	18
Intraperitoneal	18
Retroperitoneal	Right: 30 Left: 36

Detection, Diagnosis, and Screening

Because most AAAs are asymptomatic, they are incidentally generally detected during a routine clinical examination, an investigation of another disease (via chest x-ray, computed tomography (CT) scan, or echocardiogram), or a laparotomy.(120) The most common imaging devices used in the diagnosis of an AAA are magnetic resonance angiography and contrast-enhanced CT(101), with the specific aortic anatomy involved by dictating the optimal imaging protocol.

There is evidence to suggest that one-time ultrasonographic screening of men at age 65 may be sufficient to identify almost all patients who are at risk of AAA rupture.(117,121-123) A recent, large, multicentre RCT in the United Kingdom (n = 67,800 men), the Multicenter Aneurysm Screening Study, demonstrated that "one shot" screening at age 65 decreased the rate of aneurysm-related deaths within four years by 50%.(117,121) Twelve years after screening, no subject with an initial AAA diameter <2.6 cm had undergone aneurysm repair or suffered a rupture. Of those patients who did experience a rupture, all survivors had an AAA diameter <4 cm at screening. However, screening was not found to reduce overall all-cause mortality in this population.

On February 1, 2005, the U.S. Preventive Services Task Force (USPSTF) recommended screening for AAAs for men 65 to 75 years of age who had ever smoked. Screening for comparable men who have never smoked was not recommended. Screening for women was also not recommended on the basis that 1) prevalence of AAAs in women is low compared to prevalence in men; 2) peak prevalence of AAAs in women is 10 years later than it is for men, therefore occurring at ages when there are important competing causes of mortality; and 3) the available trial evidence shows no benefit from screening and repairing AAAs in women.(124,125)

Consequences of AAA Rupture

Rupture of an aneurysm is the 13th leading cause of death in the United States and one of the top 10 causes of mortality in a number of subpopulations.(126) The largest of these subpopulations is white men over age 65 (Table 30).(112,127) Estimates of the overall mortality rate following rupture of an AAA range from 15% to 94%.(128) Up to 60% of patients with ruptured aneurysms will die before reaching the hospital.(98) Over 50% of those patients who reach the hospital alive will subsequently die there as a direct result of the rupture (Table 31).(98) When operative mortality rate for AAAs are factored in, approximately 10% to 25% of individuals with a ruptured AAA survive to hospital discharge.(125)

Table 30. Subpopulations of Individuals in United States with Death Rates Resulting from Rupture of AAA Ranked in Top 10 Causes of Death during 2000

Population	Rank*	Deaths per 100,000	% of Total Deaths in Population
White males, age 66 to 74	10	2,533	1.2
Asian or Pacific Islanders, both sexes, aged over 65	10	118	1.0

Asian or Pacific Islanders, both sexes, age 75 to 84	10	92	1.0
Asian or Pacific Islanders, male, age 66 to 74	9	35	0.9
Asian or Pacific Islanders, male, age 75 to 84	10	54	1.1
Asian or Pacific Islanders, female, age 20 to 24	9	1.0	0.9
Hispanic, both sexes, age 15 to 19	10	5.0	0.3

Data extracted from National Vital Statistics Report Vol. 50; No. 15: "Deaths: Leading Causes for 2000."(127)
* Rank cause of death for population.

Table 31. Survival from Onset of Symptoms to Death in 118 Patients with Nonresected Abdominal Aortic Rupture (Darling et al. 1977)(129)

Survival Time	Number	% Alive
>6 hours	64	54%
>24 hours	51	43%
>6 days	29	25%
>6 weeks	7	6%
Not determined	14	12%

Established Treatment Options for Individuals with an AAA

Currently, no medical therapy is available that either prevents aneurysm growth or decreases the risk of rupture. Given the association between smoking and the AAA growth rate discussed above, some have argued that smoking-cessation support/therapy should be considered a noninterventional treatment option for reduction in aneurysm growth rate.(130-132) Other suggestions for controlling the expansion of AAA include moderating hypertension and lipid levels and influencing the biological processes involved in aneurysm growth. These processes include targeting inflammatory processes in the aortic wall with nonsteroidal antiinflammatory drugs (NSAIDS) and β-blockers, and treating the proteolytic activity in the aortic wall with MMP inhibitors (matrix metalloproteinases: MMP-2, MMP-8, MMP-9, and MMP-12) and doxycycline.(131-134)

Open Surgical Repair

Currently, open surgical repair is the standard of care for those undergoing prophylactic repair of a large (>5.5 cm) or rapidly expanding AAA. This major surgical procedure, which is performed under a general anesthetic, involves making a 12- to 15-inch incision in the abdomen through which the intestines are withdrawn to provide access to the aorta. Once exposed, the aorta is visually examined to determine the proper size and configuration of the synthetic graft that will be used to replace the diseased vessel. If the iliac arteries are involved, or if the amount of healthy aorta distal to the aneurysm is insufficient, a bifurcated graft is used instead of a tube prosthesis. The aorta (or the aorta and iliacs) is cross-

clamped proximal and distal to the aneurysm, and the diseased section is replaced by the prosthetic graft that is attached to the nonaneurysmal artery proximally and distally with a suture anastomosis.

Surgical AAA repair is considered high risk. Procedure-related mortality rates are about 5% to 6%, and morbidity rates range from 25% to 40%.(135) The most common morbidity class observed in patients who have undergone open surgical repair is that of cardiac complications. Major graft-related complications associated with open surgical repair, which occur in approximately 10% of patients, include anastomotic aneurysms, graft thrombosis, graft enteric erosion/fistula, graft infection, and anastomotic hemorrhage.

Because open surgery is high risk, patients with minor or no surgical risk factors and moderate-to-excellent functional capacity (ability to achieve >4 metabolic equivalents of exertion) are typically considered candidates for open surgery. In other situations, a more detailed preoperative cardiac assessment (usually with noninvasive testing) is performed to determine cardiac risk before a decision is made to proceed with AAA repair.

The presence of other medical morbidities may significantly increase the usual surgical risk (3% to 5%). For example, in the Canadian Aneurysm Study,(136) the most significant risk factor variables were electrocardiographic evidence of ischemia, COPD, and elevated creatinine levels. If none of these factors were present, operative mortality was 1.9%. However, if all these risk factors were present, 30-day mortality was 50%.

Because elective open surgical repair of an aneurysm is associated with significant morbidity and mortality, a trade-off exists between the risks associated with aneurysm rupture and the risks of surgery. Because the size of the aneurysm is the most important risk factor for a rupture, clinicians commonly use aneurysm size as a means of determining when patients should be considered for surgical repair.

The United Kingdom Small Aneurysm Trial (UKSAT) compared the outcome of 1,090 patients with AAAs between 4.0 and 5.5 cm in diameter to patients randomly assigned to receive prophylactic open surgical repair (n = 563) or ultrasound surveillance only (n = 527).(137-140) The overall hazard ratio for all-cause mortality in the UKSAT prophylactic surgery group was of borderline statistical significance compared to the surveillance group (p = 0.05). However, the 30-day postoperative

mortality rate in the surgical arm of the study was 5.5%, which led to a survival disadvantage for these patients early in the trial.(138) Survival curves for the two groups crossed at three years and at eight years; survival in the early surgery group was 7.2% higher than in the surveillance group (p = 0.03). UKSAT investigators note that this apparent benefit of early surgery cannot be directly attributed to the surgery itself, because the difference in mortality between the two arms of the study could be largely attributed to changes in lifestyle—particularly smoking cessation prompted by surgery.

Based on their findings, UKSAT investigators concluded that prophylactic open surgical repair of AAAs with a diameter <5.5 cm does not provide a long-term survival advantage over watchful waiting. Consequently, they recommended that most patients with small AAAs should have regular ultrasound surveillance rather than aneurysm repair. In addition, they recommended that aneurysm repair should only be performed when the aneurysm exceeds 5.5 cm in diameter.

The fact that UKSAT found female gender to be an independent risk factor for aneurysm rupture (rupture rates among women were four times higher than among men with similar-sized aneurysms) suggests that the recommended treatment threshold of 5.5 cm may be too high for women.(131,138) Trial data, however, did not permit the specification of a lower threshold for women. As discussed in the *Guidelines* section of this report, the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery has recommended that women undergo elective abdominal aneurysm repair at 4.5 to 5 cm aortic dilation due to the generally smaller size of the female aorta relative to the male aorta.(135)

Another study of similar design, the Aneurysm Detection and Management Veterans Affairs Cooperative Study (ADMVACS) Group, randomized 569 patients with small aneurysms (4.0 to 5.4 cm in diameter) to receive prophylactic open surgical repair and 567 patients to undergo ultrasound or CT surveillance only.(137) Patients remained in the surveillance group until their aneurysms either became symptomatic or enlarged to ≥5.5 cm. The 30-day postoperative mortality rate in this study was lower than that in the UKSAT at 2.7%. Despite this low postoperative mortality rate, the study found no statistically significant differences in survival between the two groups (relative risk, 1.21; 95% CI: 0.95 to 1.54) and no reduction in the rate of death directly related to AAA rupture in treated patients when

compared to patients allocated to the surveillance group (3.0% versus 2.6%, respectively; relative risk, 1.15; 95% CI: 0.58 to 2.31). Based on these findings, ADMVACS investigators, like UKSAT investigators, concluded that survival is not improved by elective open surgical repair of AAAs <5.5 cm in diameter.(137)

Although the risks of surgery are considered to be less than those associated with AAA rupture in patients with a large aneurysm (>5.5 cm in diameter), the risks associated with open surgical aneurysm repair remain significant. Procedure-related mortality rates are about 5% to 6%, and morbidity rates range from 25% to 40%.(139) Complications are commonly associated with previous comorbidities, the use of general anesthesia, and the duration of cross-clamp time. Consequently, there has been much effort toward finding less invasive procedures that reduce the risks associated with open surgical repair and reduce treatment expenses at the same time.

Endovascular Graft Repair

In the last 10 years, a new endovascular graft (EVG) approach to AAA repair has emerged that uses a stent. Like open surgical repair, the primary aim of this procedure is to prevent rupture of the aneurysm and thus increase survival. Preventing rupture is accomplished by positioning a graft at the site of the aneurysm, thereby excluding the aneurysm from the circulatory system. The graft is usually deployed through an incision in the femoral artery to the site of the aneurysm under fluoroscopic guidance.

Although eligibility rates for EVG repair of an AAA have increased with advances in stent and deployment technologies and increasing clinical experience, not all AAA patients are eligible for an EVG. The primary reason for ineligibility is inadequate anatomy for device delivery and placement. Women appear to be less likely than men to meet eligibility criteria.

EVG repair offers a number of potential advantages over traditional open surgical repair, including reduced surgery-related trauma and faster recovery times. However, the procedure also has a number of potential disadvantages that may limit its clinical utility. The potential disadvantages include risk of device deployment failure, endoleaks, and the need to convert an EVG procedure to open surgery.(141,142)

Watchful Waiting

Individuals with small asymptomatic aneurysms may undergo a regular CT scan, magnetic resonance imaging (MRI), ultrasound, or echocardiogram every 6 to 12 months to monitor the amount and rate of aneurysm growth. This allows for the optimum surgical treatment of the aneurysm.(101,143)

Medication

Individuals with small asymptomatic aneurysms may receive treatments, such as hyperlipidemia medications(144,145), β-blockers, and antihypertensives, to decrease blood pressure in the aorta(146,147) or potentially slow the rate of aneurysm growth.(101)

Behavior Modification

Controlling or modifying risk factors through changes in behavior (i.e., quitting smoking, controlling blood sugar and/or dietary fat, weight control and dieting for overweight or obese individuals) may all help to control the progression of the aneurysm.(101,148-150)

Clinical Practice Guidelines for Treatment of AAAs

The Joint Council of the American Association for Vascular Surgery and Society of Vascular Surgery updated the guidelines for treatment of aortic aneurysms issued in 1993 with the publication of a new set of recommendations for the operative management of AAAs in 2003.(135) In summary, the panel made the following recommendations for AAA repair:

- The arbitrary setting of a single threshold diameter for elective AAA repair applicable to all patients is not appropriate, because the decision for repair must be individualized in each case.
- Randomized trials have shown that the risk of rupture of small (<5 cm) AAA is quite low, and a policy of careful surveillance up to a diameter of 5.5 cm is safe unless rapid expansion (>1 cm/year) or symptoms develop. However, early surgery is comparable to surveillance with later surgery so that the patient preference is important—especially for AAA 4.5 cm to 5.5 cm in diameter.
- Based on best available current evidence, a 5.5 cm diameter appears to be an appropriate threshold for repair in the average patient. However,

subsets of younger low-risk patients, with long projected life expectancy, may prefer early repair. If the surgeon's personal documented operative mortality rate is low, repair may be indicated at smaller sizes (4.5 cm to 5.5 cm) if that is the patient's preference.

- For women, or AAA with greater than average rupture risk, elective repair at 4.5 cm to 5.0 cm is an appropriate threshold for repair.
- For high-risk patients, delay in repair until larger diameter is warranted, especially if endovascular aneurysm repair (EVAR) is not possible.
- In view of its uncertain long-term durability and effectiveness, as well as the increased surveillance burden, EVAR is most appropriate for patients at increased risk for conventional open aneurysm repair.
- EVAR may be the preferred treatment method for older, high-risk patients, those with "hostile" abdomens, or other clinical circumstances likely to increase the risk of conventional open repair—if their anatomy is appropriate.
- Use of EVAR in patients with unsuitable anatomy markedly increases the risk of adverse outcomes, need for conversion to open repair, or AAA rupture.
- At present, there does not appear to be any justification that EVAR should change the accepted size thresholds for intervention in most patients.
- In choosing between open repair and EVAR, patient preference is of great importance. It is essential that the patients are well informed to make such choices.

Acknowledging the lack of a precise formula to predict exact rupture risk from risk factors, the panel paper utilized the following table of rupture risks suggested by Schermerhorn and Cronenwett (Table 32).(151)

Table 32. AAA Rupture Risk*

Rupture Risk	Low Risk	Average Risk	High Risk
Diameter	<5 cm	5 – 6 cm	>6 cm
Expansion	<0.3 cm/year	0.3 – 0.6 cm/year	>0.6 cm/year
Smoking / COPD	None, mild	Moderate	Severe / steroids
Family History	No relatives	One relative	Numerous relatives
Hypertension	Normal blood pressure	Controlled	Poorly controlled
Shape	Fusiform	Saccular	Very eccentric
Wall Stress	Low (35 N/cm^2)	Medium (40 N/cm^2)	High (45 N/cm^2)
Gender	-----	Male	Female

* adapted from Schermerhorn, MI Cronenwett JL Decision making in vascular surgery. Philadelphia, WB Saunders Co. 2001
COPD Chronic obstructive pulmonary disease.

As has been discussed earlier, the panel paper recognized the lack of precise data on rupture risk, and added the caveat that the true natural history of untreated AAA, including risk factors for rupture, are still poorly defined.

Identification of Evidence Base

The purpose of this section is to systematically review the data pertaining to the risk factors associated with AAA rupture with the aim of informing FMCSA about the factors that have been shown to predict which individuals with an AAA are most at risk for sudden incapacitation due to AAA rupture. In attempting to address this issue we searched for studies of any design that attempted to identify risk factors for AAA rupture. These studies included case-control trials, case series, controlled trials in which a group of individuals with an AAA did not receive treatment, and natural history studies. Our decision to include studies of any design was motivated by the fact that we were aware that data on the risk factors for AAA rupture would be rare.(152) As noted by Brewster, "Accurate data on rupture risk are likely the least precise of the several variables which need to be assessed in the decision-making process. This is due to the fact that in the past three decades few patients have been followed without intervention; hence, the true natural history of untreated AAA remains somewhat poorly defined."(135)

The identification of the evidence user in this section of the evidence report is presented in Figure 15. Our searches[15] identified a total of 90 articles that appeared relevant. Following application of the retrieval criteria for this question, 90 full-length articles were retrieved and read in full. Fourteen of these 90 retrieved articles were found to meet our criteria for inclusion[16] (Table 33). These 14 articles described a total of 14 independent studies.

Table D-2 in Appendix D lists the 76 articles that were retrieved but then excluded, and it provides the reason for their exclusion. Detailed information pertinent to this section that has been extracted from the included studies is presented in Study Summary Tables that can be found in Appendix G.

[15] See Appendix A for search strategies.

[16] See Appendix C for inclusion criteria.

Figure 15. Development of Evidence Base for Key Question 2

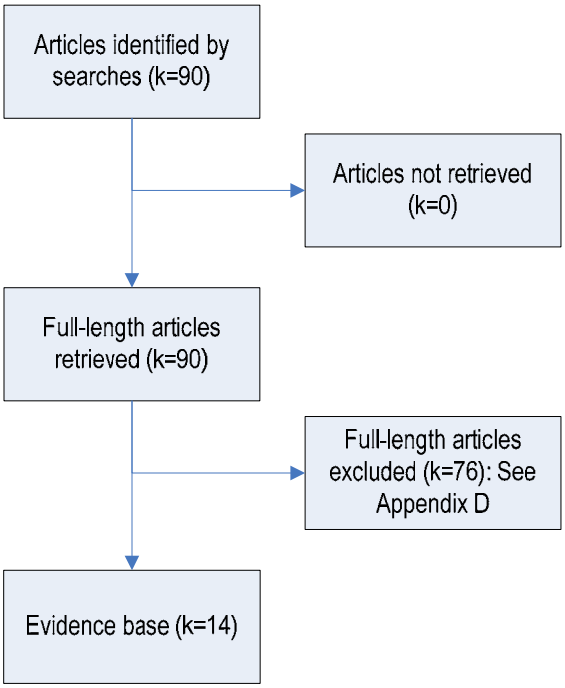


Table 33. Evidence Base for AAA

Primary Reference	Year	Study Location	Country
Fillinger et al.(153)	2004	New Hampshire	USA
Brown et al.(154)	2003	Ontario	Canada
Fillinger et al.(155)	2003	New Hampshire and Iowa	USA
Lederle et al.(156)	2002	Multicenter (47 Veterans Affairs Medical Centers)	USA
Stenbaek et al.(157)	2000	Stockholm	Sweden
Jones et al.(158)	1998	Enfield	UK
Reed et al.(159)	1997	Colorado	USA
Schewe et al.(160)	1994	München	Germany
Faggioli et al.(161)	1994	New York	USA
Guirguis and Barber(162)	1991	Ottawa	Canada

Primary Reference	Year	Study Location	Country
Sterpetti et al.(1)	1991	Rome	Italy
Nevitt et al.(163)	1989	Minnesota	USA
Cronenwett et al.(164)	1985	New Hampshire	USA
Darling et al.(119)	1977	Massachusetts	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 14 studies that met the inclusion criteria for this key question. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Detailed information pertinent to this section that has been extracted from included studies is presented in the *Study Summary Tables* that can be found in Appendix G.

The primary characteristics of the 14 included studies that address Key Question 1 are presented in Table 34. Eight studies were prospective; six were retrospective. Most of the articles ascertained the rate of aortic aneurysm rupture in a cohort of individuals and attempted to identify risk factors associated with a rupture event.

Table 34. Key Study Design Characteristics of Studies that Address Key Question 1 – AAA

Reference	Year	Size	Study Design	Prospective or Retrospective	Potential Risk Factors Assessed	Analyses Used to Identify Risk Factors
Fillinger et al.(153)	2004	259	Case Control	Retrospective	Aortic tortuosity (angulation of the aortic blood vessel) Age Gender Known heart disease COPD Smoking Family history of AAA Diabetes mellitus History of hypertension Blood pressure: diastolic and systolic Creatinine concentration	Multivariate logistic regression
Brown et al.(154)	2003	476	Cohort	Prospective	Initial aortic diameter Aortic expansion rate Gender	Cox proportional hazards regression model

Reference	Year	Size	Study Design	Prospective or Retrospective	Potential Risk Factors Assessed	Analyses Used to Identify Risk Factors
Fillinger et al.(155)	2003	103	Cohort	Retrospective	Initial aortic diameter Peak aortic wall stress Gender Age Blood pressure: diastolic and systolic Known heart disease COPD Creatinine concentration	ANOVA; Kaplan-Meier analysis; Proportional hazards analysis with stepwise regression; ROC analysis
Lederle et al.(156)	2002	198	Cohort	Prospective	Aortic diameter Renal artery involvement of the AAA Weight Smoking Myocardial Infarction Coronary artery bypass surgery Age Family history of AAA Blood pressure: diastolic and systolic COPD Use of beta blockers Poor medical condition	Incidence; Cox regression model
Stenbaek et al.(157)	2000	67	Cohort	Prospective	Maximum aortic diameter Aortic surface area Thrombus area	Mann-Whitney U test and Chi-square with Fisher's exact test
Jones et al.(158)	1998	192	Cohort	Prospective	Aortic diameter	Kaplan-Meier survival curve
Reed et al.(159)	1997	181	Cohort	Retrospective	Aortic diameter (initial and at last ultrasound) Aortic aneurysm expansion rate	Pearson correlation coefficient Kaplan-Meier analysis using log rank
Schewe et al.(160)	1994	199	Cohort	Prospective	Initial aortic diameter Age Cholesterol High- and low-density lipoproteins Smoking history Blood pressure: diastolic, systolic, and pulse pressure	Kaplan-Meier product limit method. Mann-Whitney/Wilcoxon's U test
Faggioli et al.(161)	1994	135	Cohort	Prospective	Endoluminal thrombus Aortic wall Saccular outpouching (blister)	Chi-square Fisher's Exact Test Multiple logistic regression
Guirguis and Barber(162)	1991	300	Cohort	Prospective	Aneurysm expansion rate	Kaplan-Meier life-table analysis Exact binomial test

Reference	Year	Size	Study Design	Prospective or Retrospective	Potential Risk Factors Assessed	Analyses Used to Identify Risk Factors
Sterpetti et al.(1)	1991	297	Cohort	Retrospective	Hypertension Aortic diameter Bronchiectasis Emphysema Smoking History of chronic bronchitis Gastric ulcer Simultaneous cancer Aortic aneurysm shape Age Gender Diabetes mellitus Aneurysm location Myocardial hypertrophy Renal artery disease Lower limb artery Disease (carotid, hepatic cirrhosis, pancreatitis)	Stepwise logistic regression
Nevitt et al.(163)	1989	370	Cohort	Retrospective	Initial aortic diameter Rate of aortic diameter change Age Gender	Kaplan-Meier survival analysis Cox proportional hazards analysis
Cronenwett et al.(164)	1985	473	Cohort	Prospective	Age Gender Blood pressure: diastolic and systolic Smoking Lipids Renal function Initial aneurysm diameter Last aneurysm diameter Interval between first and last diameter Follow-up interval Expansion rate Proximal aorta diameter Initial aneurysm diameter + proximal aortic diameter Aneurysm expansion rate + proximal aortic diameter Symptoms at presentation Aneurysm discovery by physical examination or radiograph Reason not operated COPD Cardiac disease	Not listed
Darling et al.(119)	1977	67	Cohort	Retrospective	Aortic diameter Diffuse atherosclerotic disease Age Gender	Cox proportional hazards model

AAA Abdominal aortic aneurysm.
ANOVA Analysis of variance
COPD Chronic obstructive pulmonary disease.
ROC Receiver operating characteristic.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 2 are presented in Table 35. This assessment found that the quality of the included studies was not high. Six of the 14 included studies were graded as moderate quality. The remaining eight studies were graded as low quality. Note that even though some studies scored highly, these studies used case-control or cohort study designs. Case-control studies, by virtue of their retrospective design, are susceptible to bias. Therefore, even a perfectly designed and executed case-control study cannot be graded as high quality. Cohort studies can be either prospective or retrospective, and are susceptible to bias through differences in patient selection, follow-up, and measurement bias (particularly in how measurements are taken and how the data is analyzed). Therfore, a well-designed cohort study cannot be graded as high quality. Other factors that differentiated moderate- from low-quality studies included poor reporting, failure to adjust for exposure differences such as the length of time each study participant had had an aneurysm, and questions regarding whether certain studies had achieved the statistical power necessary to investigate a rare event such as aneurysm rupture.(152)

Table 35. Quality of Studies of AAA Rupture Risk

Reference	Year	Quality Scale Used	Quality Score	Quality
Fillinger et al.(153)	2004	Newcastle-Ottawa Quality Assessment Scale	8.75	Moderate
Brown et al.(154)	2003	Newcastle-Ottawa Quality Assessment Scale	8.75	Moderate
Fillinger et al.(155)	2003	Newcastle-Ottawa Quality Assessment Scale	7.75	Moderate
Lederle et al.(156)	2002	Newcastle-Ottawa Quality Assessment Scale	7.75	Moderate
Stenbaek et al.(157)	2000	Newcastle-Ottawa Quality Assessment Scale	9.75	Moderate
Jones et al.(158)	1998	Newcastle-Ottawa Quality Assessment Scale	7.75	Low
Reed et al.(159)	1997	Newcastle-Ottawa Quality Assessment Scale	7.75	Low
Schewe et al.(160)	1994	Newcastle-Ottawa Quality Assessment Scale	5.75	Low
Faggioli et al.(161)	1994	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Guirguis and Barber(162)	1991	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Sterpetti et al.(1)	1991	Newcastle-Ottawa Quality Assessment Scale	7.75	Low
Nevitt et al.(163)	1989	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Cronenwett et al.(164)	1985	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Darling et al.(119)	1977	Newcastle-Ottawa Quality Assessment Scale	8.75	Moderate
		Overall Quality	8.26	Moderate

The reported risk of aortic aneurysm rupture varies considerably in the literature. Part of this variation lies in what Reed et al.(159) identified as the potential for bias, specifically referral bias (studies conducted at facilities where patients may have

been referred for care or treatment on the basis of symptoms or aneurysm growth) and selection bias (studies in which patients were not randomly selected, but may overrepresent sudden, unexplained deaths). In addition, Reed et al. questioned the inclusion of aneurysms of varying size at rupture in the same cohort. They did so without including accurate information about aneurysm growth over time. Such an error might cause clinicians to overestimate the risk of rupture in the near future for certain size aneurysms, leading to premature or unnecessary exposure to the risks present in aortic aneurysm surgery (paraplegia and paraparesis being two examples). Brewster et al.(135) cite the paucity of natural history studies for untreated AAAs (due to the lack of patients who have not experienced some form of intervention in studies conducted over the last 30 years), which leave little to no accurate data available to understand true aortic rupture risk.

An additional challenge to literature synthesis is the wide variety of populations included in the estimate of rupture risk. Some studies included only those individuals who were not eligible for intervention due to comorbidity(165) or who had refused treatment, while other studies included all those eligible for screening CT—details which compounded an already very heterogenous study base. Rizzo et al. noted discrepancies in the statistical methods used to study TAA that may result in inaccurate information, giving particular attention to the possibility of measurement error (error introduced into the study through interobserver variation, and through the use of multiple diagnostic modes).(166)

As summarized by Griepp et al.:

> *"It has been difficult to extract information relevant for future patient care from studies of the natural history of aneurysms for several reasons. Most studies have included a mixture of different proportions of patients with aneurysms with different etiologies, different locations within the thorax, at varying intervals from acute onset, classified by several conflicting and overlapping systems of nomenclature. The completeness and accuracy of follow-up is also variable, so that is often difficult to be sure whether deaths occurred from rupture or from other causes. Recent improvements in the results of surgery resulted in the withdrawal of increasing numbers of patients for elective surgery, even in the most careful, rigorous studies. The removal of these patients weakens our ability to assess the possible contribution to rupture risk of factors that are frequent indications for*

surgery, such as aneurysm size, extent, growth rate, and the presence of pain."(167)

Due to the heterogeneity introduced through the use of very different populations, lack of standardization, referral bias, and selection bias, the relationship of risk factors to aortic rupture could not be quantified in this report.

Generalizability of Evidence to Target Population

None of the studies featured in this section of the Cardiovascular report specifically included information about the occupations of the participants, thus making it impossible to generalize on the basis of employment. As acknowledged in the *Study Design* section, the heterogeneity of the populations represented in the included studies also precludes us from making a definitive statement about the generalizability of the evidence to the target population (CMV drivers).

Findings

As outlined in the previous section on study design, heterogeneity in the data as a result of numerous factors (use of very different populations, lack of standardization, referral bias, and selection bias) make the relationship of risk factors to aortic rupture unable to be quantified in this report.

As demonstrated by the data presented in Table 36 and Table 37, AAA rupture risk appears to be related to a number of independent factors, including AAA size, COPD, the presence of hypertension, AAA expansion rate, smoking status, aortic wall stress, aortic tortuosity, bronchiectasis, and female gender. The most important and consistently identified independent risk factor for AAA rupture is aneurysm size.

Table 36. Results of Studies on Rupture of an AAA

Study	Year	Size	Model	Univariate	Multivariate
Fillinger et al.(153)	2004	259	Multivariate logistic regression	Group with ruptured AAA = RUP Significant variables: • Currently smoking • History of hypertension • Maximum AAA diameter • Mean diameter for ruptured AAA was 5mm smaller for females • RUP had slightly larger supraceliac aortic diameter • RUP were less likely to have moderate to severe aortic tortuosity • RUP had more aortic diameter asymmetry	Significant variables: • Aortic tortuosity • Cross-sectional diameter asymmetry • Current smoking
Brown et al.(154)	2003	476	Cox proportional hazards regression model	NR	Significant variable: • Aneurysm diameter Association between aneurysm diameter showed a progressive relative risk of rupture with increasing diameter. Relative risk of rupture in males with aneurysm 5.0 – 5.9 cm diameter was 1% per year; relative risk of females with aneurysm 5.0-5.9 cm diameter was 4 times higher (RR 4.0). Average annual risk of rupture in men with AAA 6cm or greater was 14.1%, and in females was 22.3%.
Fillinger et al.(155)	2003	103	ANOVA; Kaplan-Meier analysis; Proportional hazards analysis with stepwise regression; ROC analysis	Rupture/Symptomatic group had higher diastolic and systolic blood pressure. ROC curves for predicting rupture were worse for diameter than for peak wall stress, with both curves being significant compared to the null hypothesis.	Significant variables: • Peak wall stress • Gender Peak wall stress and gender were the only significant independent predictors of rupture risk over time, with stress demonstrating more significance (RR 25x, 95% CI 5.7 – 110x) than female gender (RR 3x, 95% CI 1.3 – 7.4). There was no significant interaction between the two variables. To evaluate the effect of blood pressure versus 3-D shape on stress, maximum peak wall stress, at actual systolic blood pressure, was manually removed as a variable, and stress at uniform pressure (120 mm Hg) was added. Stress and gender remained the dominant factors, with systolic blood pressure now also a significant independent variable. When all stress-related and 3-D shape related variables were purposely removed from analysis, diameter, systolic blood pressure, and gender were all retained as significant variables – that was the only method by which diameter could be retained. In this scenario, RR for rupture was 9x for large (>5.5 cm) aneurysm.

Study	Year	Size	Model	Univariate	Multivariate
Lederle et al.(156)	2002	198	Incidence; Product limit estimates; Cox regression model	1 year incidence of probable rupture by initial aneurysm diameter: 5.5 – 5.9cm: 9.4% 6.0 – 6.9 cm: 10.2% 6.5 – 6.9 cm: 19.1% ≥7 cm: 32.5%	Significant variables: • Aortic diameter Diameter of AAA was the strongest predictor of rupture in terms of variance explained (RR 1.39 per 1 cm; 95% CI 1.11 – 1.73) After adjustment for AAA diameter at entry, the following other factors were also significant predictors of rupture: • Renal artery involvement of the AAA (RR 2.36, 95% CI, 1.12 – 4.97) Lower weight (RR 0.75 per 10 kg, 95% CI 0.61- 0.91) • No history of smoking (RR 0.30, 95% CI 0.11-0.84) • No myocardial infarction (RR 0.46, 95% CI 0.24-0.88) • No coronary artery bypass graft surgery (RR 0.30, 95% CI 0.96 – 1.05)
Stenbaek et al.(157)	2000	67	Mann-Whitney U test and Chi-square with Fisher's exact test		There was a significantly higher increase of thrombus area among the seven patients that ruptured. No corresponding significant difference in growth of diameter was seen. Forty patients had an increase of diameter less than 0.5 cm per year, of whom 4 (10%) experienced rupture versus 3 of 12 (25%) with a diameter increase exceeding 0.5 cm/year (ns). When looking at increase of surface area, 5/27 (19%) with an increase >2 cm^2 year ruptured. The corresponding figure for patients with <2 cm^2 increase/year was 2.25 (8%). Among those with an increase in thrombus area >1.5 cm^2/year, 6/24 (2%) experiences rupture compared with only 1 of 23 (4%) with a lower increase. This implies a sensitivity of 86% and a specificity of 55% for predictions of rupture in the group with an increase of thrombus area >1.5 cm^2. Among those that lacked thrombus at the last examination none experienced rupture, whereas 7 of 41 (17%) with varying degrees of thrombus experienced rupture.
Jones et al.(158)	1998	192	Kaplan-Meier survival curve	Incidence of rupture in the first 2 years from aneurysm diagnosis of 5.0-5.9 cm. Some may have enlarged further before rupture. Cumulative rupture rate: Smaller AAA (5.0 – 5.9): 28 (95% CI 12- 49) Larger AAA (≥6 cm): 41 (95% CI 24 – 59)	NR
Schewe et al.(160)	1994	199	Kaplan-Meier product limit method. Mann-Whitney/Wilcoxon U test	Positive correlation between aneurysmal diameter at initial examination and expansion rate (r = 0.266, p = 0.02), with considerable variation among expansion rates among aneurysms of the same size. Expansion rate increased significantly with rising systolic (r = 0.236, p = 0.011) and diastolic blood pressure (r = 0.294, p = 0.001)	Significant variable: • Aneurysm diameter above 5 cm Comparison of possible predictors of rupture between patients with ruptured and patients with non-erupted aneurysm (U test)*

Study	Year	Size	Model	Univariate	Multivariate
Faggioli et al.(161)	1994	135	Chi-square Fisher's exact test Multiple logistic regression	Incidence of frank rupture among aneurysms <5 cm in diameter was 9%.	Significant variable: • Presence of a saccular outpouching (i.e., blister, a small area of localized further dilation within the aneurysm)
Guirguis et al.(162)	1991	300	Kaplan-Meier life-table analysis Exact binomial test	Cumulative incidence of rupture at 10 months: 1% and 0% for patients with aneurysms <4 cm and 4.0 – 4.9 cm 8% for patients with aneurysms 5 cm or larger Cumulative incidence of rupture at 6 years: 1% to 2% for patients with aneurysms <4 cm and 4.0 – 4.9 cm 20% for patients with aneurysms 5 cm or larger	Significant variable: • Aneurysm diameter above 5 cm
Sterpetti et al.(1)	1991	297	Stepwise logistic regression	NR	Significant variables: • Aneurysm diameter • Presence of arterial hypertension • Presence of bronchiectasis
Nevitt et al.(163)	1989	370	Kaplan-Meier survival analysis Cox proportional hazards analysis	Cumulative rupture incidence (after initial ultrasound documentation of aneurysm): 6% at 5 years 8% at 10 years Cumulative rupture incidence (aneurysms of 5 cm or larger): 25% at 8 years Cumulative rupture incidence (aneurysms of 3.5 – 4.9 cm diameter): 5% at 9 years Cumulative rupture incidence (aneurysms of <3.5 cm diameter): 0% at 8 years	Significant variables: • Larger aneurysm initial diameter 1 cm larger initial diameter was associated with an increase of approximately 50% in the adjusted risk of rupture (adjusted hazard ratio 1.55; 95% CI 1.04 – 2.32)
Darling et al.(119)	1989	473	Not listed	Rate of rupture: Aneurysm 4.1 – 7.0 cm: 25% Aneurysm 7.1 – 10.0 cm: 45% Aneurysm >10.0 cm: 60%	Significant variables: Relationship of diameter to rupture: ≤4 cm: 9.5% 4.1 – 5.0 cm: 23.4% 5.1 – 7.0 cm: 25.3% ≥10.1: 60.5%
Cronenwett et al.(164)	1985	67	Cox proportional hazards model	NR	Significant variables: • COPD (most significant) • Initial aneurysm diameter in the AP dimension • Diastolic blood pressure

AAA Abdominal aortic aneurysm.
AP Antiposterior.
ANOVA Analysis of variance

CI Confidence interval.
COPD Chronic obstructive pulmonary disease.
NR Not reported.
RR Rate ratio.
RUP Group with ruptured AAA.

***Table 1 from Schewe et al.(160)**

Variable	Ruptured (n = 8)	Nonruptured (n = 191)	*P*
Systolic blood pressure (mmHg)	176.00 ±37.81	153.85 ±23.31	0.198
Diastolic blood pressure (mmHg)	98.00 ±16.43	86.46 ±12.47	0.135
Amplitude of blood pressure (mmHg)	78.00 ±24.89	67.39 ±18.12	0.458
Mean expansion rate (cm/year)[a]	0.47 ±0.23	0.23 ±0.26	0.013
Diameter at last measurement (cm)	7.28 ±1.70	6.14 ±1.56	0.036
Diameter at initial measurement (cm)	5.58 ±1.92	3.92 ±1.21	0.007
Total cholesterol (mg/dL)	235.20 ±34.25	246.32 ±62.13	0.627
Smoking history (pack-years)	14.00 ±15.16	23.17 ±24.88	0.476
Age at entry (years)	71.91 ±7.92	69.77 ±8.54	0.479
Observation period (years)	3.63 ±2.76	2.65 ±3.23	0.177

Table 37. Independent Risk Factors for Rupture of an AAA

Study	Year	Risk Factors																	
		Aneurysm Diameter	Pain	Diameter Asymmetry	Family History	Aneurysmal Stiffness	Serum Triglyceride	Gender	Smoking Status	Expansion Rate	Wall Stress	Aortic Tortuosity	Aortic Outpouching	Heart/Coronary Artery Disease	Hypertension History	COPD	Creatinine	Bronchiectasis	Age
Fillinger et al.(153)	2004								✓			✓							
Brown et al.(154)	2003							✓		✓									
Fillinger et al.(155)	2003							✓			✓								

Study	Year	Risk Factors																	
		Aneurysm Diameter	Pain	Diameter Asymmetry	Family History	Aneurysmal Stiffness	Serum Triglyceride	Gender	Smoking Status	Expansion Rate	Wall Stress	Aortic Tortuosity	Aortic Outpouching	Heart/Coronary Artery Disease	Hypertension History	COPD	Creatinine	Bronchiectasis	Age
Lederle et al.(156)	2002	✓																	
Stenbaek et al.(157)	2000	✓								✓									
Jones et al.(158)	1998	✓																	
Reed et al.(159)	1997	✓																	
Schewe et al.(160)	1994	✓								✓									
Faggioli et al.(161)	1994												✓						
Guirguis and Barber(162)	1991	✓																	
Sterpetti et al.(1)	1991	✓													✓			✓	
Nevitt et al.(163)	1989	✓																	
Cronenwett et al.(164)	1985	✓													✓	✓			
Darling et al.(119)	1977	✓																	

✓ risk factor studied, found to be a significant risk factor.
COPD Chronic obstructive pulmonary disease.

The most important risk factor for AAA rupture appears to be aneurysm diameter. The larger the diameter of the aneurysm, the more likely it is to rupture (Table 38). Based on the last aneurysm measurement by ultrasound, Reed et al. estimated the risk of rupture to be 0% for AAAs <4.00 cm, 1.0% for AAAs between 4.00 cm and 4.99 cm, 11% for AAAs between 5.00 and 5.99 cm in diameter, and 26% for AAA between 6.00 cm and 6.99 cm in diameter.(159) Jones et al.(158) found that the risk of rupture was 28% within three years of the diagnosis of an AAA among patients with AAAs 5.0 cm to 5.9 cm in diameter and who were considered unfit for open surgery. This risk increased to 41% for patients with AAAs ≥6.0 cm in diameter.(158) Brown et al. demonstrated that the relative risk for aortic aneurysm rupture increased from 1% (5.0 cm to 5.9 cm) to 14.3% (6.0 cm to 6.9 cm) in males, and from 4% (5.0 cm to 5.9 cm) to 22.6% (6.0 cm to 6.9 cm) in females.(154)

Table 38. Risk Stratification Derived from AAA Evidence Base

Study	Year	N =	Risk Stratification by Abdominal Aortic Aneurysm Size
Fillinger et al.(153)	2004	259	Not Calculated
Brown et al.(154)	2003	476	Men, 5.0 to 5.9 cm: 1.0 RR (95% CI) Women, 5.0 to 5.9 cm: 4.0 RR (1.2, 13.0 95% CI) Men, 6.0 cm or greater: 14.3 RR (5.9, 34.5 95% CI) Women, 6.0 or greater: 22.6 RR (8.4, 61.1 95% CI)
Fillinger et al.(155)	2003	103	Not Calculated
Lederle et al.(156)	2002	198	Not Calculated
Stenbaek et al.(157)	2000	67	Not Calculated
Jones et al.(158)	1998	192	Three years of diagnosis in patients considered unfit for open surgery. 5.0 – 5.9 cm: 28%
Reed et al.(159)	1997	181	Estimate of rupture risk by aneurysm diameter at last ultrasound Ruptures/Patient Year <3 cm: 0, CI 0.00 – 0.08 3.0 – 3.9 cm: 0, CI 0.00 – 0.05 4.0 – 4.99 cm: 0.007, CI 0.00 – 0.05 5.0 – 5.99 cm: 0.11, CI 0.01 – 0.21 6.00 – 6.99 cm: 0.26, CI 0.07 – 0.46
Schewe et al.(160)	1994	199	Not Calculated
Faggioli et al.(161)	1994	135	Not Calculated
Guirguis et al.(162)	1991	300	Not Calculated
Sterpetti et al.(1)	1991	297	Not Calculated
Nevitt et al.	1989	370	Not Calculated
Darling et al.(119)	1989	473	Not Calculated
Cronenwett et al.(164)	1985	67	Not Calculated

CI Confidence interval.
RR Rate ratio.

Time to Rupture of an AAA

Much of the research devoted to AAAs has revolved around developing guidelines for intervention in which the risks of surgery are balanced against the understanding that

most aortic aneurysms do not rupture *and* the risk that rupture may occur in a given individual at a given time. Based on the understanding that aneurysm diameter is the predominant risk factor for aneurysm rupture, and that diameter can increase over time, determining the rate at which an aneurysm may grow and the incidence of rupture risk by diameter of the aneurysm provides important information in deciding when the risks of rupture outweigh the risks inherent in elective surgical intervention. As outlined earlier in this report by Griepp,(167) however, the natural history of aortic aneurysms is largely unknown due to the more efficient methods of diagnosis and treatment that have been made available over the last three decades, making for a lack of information on incidence of rupture by aneurysm diameter. In Lederle et al.(156), this dearth of information was addressed in a prospective cohort study of the incidence of rupture based on the AAA diameter at first examination and on attained AAA diameter. In examining aneurysm diameter, Lederle et al. established that the larger the aneurysm was at discovery, the greater the cumulative incidence of rupture was over time. Similarly, the incidence of rupture increased with the attained diameter of the aortic aneurysm. The results of this study are detailed in Table 39 and Table 40.

Table 39. Cumulative Incidence of Rupture by Initial AAA Diameter*

Type of Rupture Event	Follow-up, mo						
	6	12	18	24	30	36	42
Patients with AAA 5.5-5.9 cm (n = 61)							
Definite (n = 7)	3.5	5.5	11.8	16.4	22.4	22.4	. . .
Probable (n = 11)	3.5	9.4	17.7	22.1	27.6	27.6	. . .
Possible(n = 15)	3.5	9.4	22.4	26.5	35.7	35.7	. . .
Patients with AAA 6.0-6.9 cm (n = 85)							
Definite (n = 13)	3.8	7.5	7.5	16.5	24.2	24.2	32.7
Probable (n = 17)	5.0	10.2	10.2	18.9	26.5	32.1	47.2
Possible (n = 19)	5.0	10.2	10.2	21.4	28.8	37.9	51.7
Patients with AAA ≥7.0 cm (n = 52)							
Definite (n = 15)	11.0	27.9	34.4	39.5	. . .	. . .	. . .
Probable (n = 17)	11.0	32.5	38.7	43.4	. . .	. . .	. . .
Possible (n = 18)	12.8	34.0	40.0	44.6	. . .	. . .	. . .

* Data are given as percentages. AAA indicates abdominal aortic aneurysm; ellipses, data not shown (for instances in which <10 patients remained in observation at the beginning of the interval). Definite ruptures were confirmed by autopsy, surgery, or computed tomographic scan. Probable ruptures were defined as definite ruptures plus cases of death with symptoms consistent with AAA rupture and cases of repair of symptomatic unruptured AAA. Possible ruptures were defined as all probable ruptures plus cases of sudden unexplained/unwitnessed deaths.

Table 40. Cumulative Incidence of Rupture by Attained AAA Diameter*

Type of Rupture Event	Follow-up, mo				
	6	12	18	24	30
Patients with AAA 5.5-5.9 cm (n = 61)					
Definite (n = 4)	3.6	6.4	15.0	. . .	. . .

Probable (n = 6)	3.6	12.0	20.0	. . .	. . .
Possible (n = 7)	3.6	12.0	25.3	. . .	. . .
Patients with AAA 6.0-6.9 cm (n = 113)					
Definite (n = 6)	2.0	3.8	6.5	13.5	13.5
Probable (n = 8)	3.0	6.1	8.8	15.6	15.8
Possible (n = 11)	3.0	7.4	10.0	20.2	20.2
Patients with AAA ≥7.0 cm (n = 107)					
Definite (n = 25)	11.0	23.4	28.7	31.8	37.1
Probable (n = 31)	11.9	29.2	34.1	37.0	47.1
Possible (n = 34)	14.0	30.9	35.7	41.0	50.5

* Data are given as percentages. Patient could be evaluated in more than 1 stratum in this analysis, but events are counted only once. AAA indicates abdominal aortic aneurysm; ellipses, data not shown (for instances in which <10 patients remained in observation at the beginning of the interval). Definite ruptures were confirmed by autopsy, surgery, or computed tomographic scan. See Table 2 footnote for rupture definitions.

Rupture-Risk Models for AAA

Currently, the literature on abdominal aortic rupture risk contains two models, both of which are centered around aortic wall stress and wall mechanics. In Fillinger et al.,(168) it was established that peak wall stress calculated in vivo for AAAs near the time of rupture were significantly higher than peak wall stress encountered in AAAs that had undergone elective aneurysm repair. It was suggested that computer 3-dimensional modeling of wall stress might provide a more accurate method of predicting rupture risk than AAA diameter. Sonesson et al. concluded that there was no difference in aneurysmal wall mechanics (estimated as stiffness, which was calculated from aortic diameter and pulsatile diameter change) between AAAs that subsequently ruptured and AAAs that underwent elective repair, meaning that rupture risk could not be predicted by aortic aneurysm wall stiffness.(169)

Section Summary

The most commonly identified risk factor for AAA is aneurysm size (Strength of Evidence: Moderate)

- **Due to the fact that there were a number of methodologic problems involving heterogeneity of the populations studied, biases, statistical power issues, and a lack of standardization regarding aneurysm measurement and reporting, no attempt was made to construct a quantitative model describing the risk for rupture for an aortic aneurysm or TAA.**

  Fourteen (Total N = 3,317) moderate-quality studies assessed the potential risk factors for rupture of an abdominal aneurysm. These 14 studies demonstrated that aneurysm size was the most important risk factor associated with aneurysm rupture

(n = 10 studies). Other risk factors for abdominal aortic rupture identified included COPD (n = 1 study), presence of hypertension (n = 2 studies), AAA expansion rate (n = 3 studies), smoking status (n = 1 study), aortic wall stress (n = 1 study), aortic tortuosity (n = 1 study), bronchiectasis (n = 1 study), aortic outpouching (n = 1 study), and female gender (n = 2 studies).

TAAs and Risk for Rupture

Background

TAAs are less common than abdominal aneurysms.(101) As with an abdominal aneurysm, a thoracic aneurysm represents a weakened area of the aorta that responds to the continual stress imposed by the constant ejection of blood from the heart through localized expansion of the aortic vessel walls (Table 41). These dilated areas in the aortic wall are specifically located in the ascending thoracic aorta, aortic arch, or the descending thoracic aorta. A continuous aneurysm that extends throughout these areas and into the abdomen is referred to as a thoracoabdominal aneurysm. The descending thoracic aorta is most commonly affected by aneurysms (50%), followed by the ascending segment (25%) and the aortic arch (25%), with the location associated with the etiology, natural history, and treatment of the aneurysm (Figure 16).

Table 41. Locations and Factors Associated with TAA Development

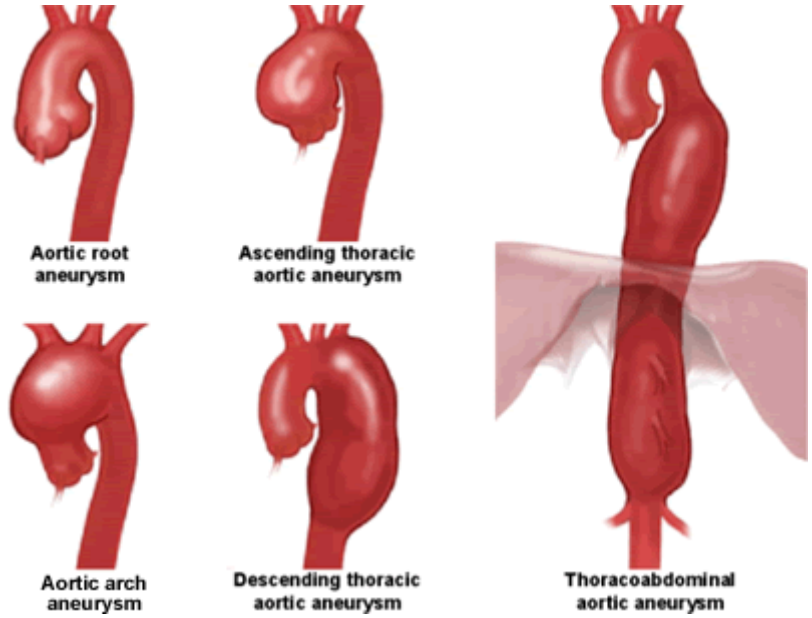
Location of Aneurysm	Causes associated with Aneurysm Type
Ascending Thoracic Aneurysm (aortic root aneurysm and supravalvular aortic aneurysm)	Cystic medial degeneration (necrosis) Genetic disorders (Marfan syndrome; Ehlers-Danlos syndrome) Family history of thoracic aortic aneurysm Atherosclerosis Infection (syphilis, tuberculosis) Trauma
Aortic Arch Aneurysm	Takayasu's arteritis Atherosclerosis Continuation of ascending and/or descending aortic aneurysm Trauma
Descending Thoracic Aortic Aneurysm (often distal to the left subclavian artery and proximal to the celiac axis)	Atherosclerosis, including risk factors for this disease such as: Age (≥55) Male gender Family history Genetic factors Hyperlipidemia Hypertension Smoking Diabetes Trauma

The point at which a dilated segment of the thoracic aorta becomes an aneurysm is not entirely clear and several definitions exist in the literature. The most common definitions of a TAA are as follows:

1. The localized enlargement is equal to or greater than twice the normal vessel diameter.
2. Dilation of the aorta is ≥150% of its normal diameter for a given segment.
3. A dilation exceeding the maximum diameter of the aorta at ≥4.9 cm (mild ectasia 3.9 to 4.4 cm; moderate ectasia 4.5 to 4.9 cm)

True thoracic aneurysms may be distinguished from pseudoaneurysms by their tissue involvement. A true aneurysm involves all three layers of the blood vessel wall (the intima, the media, and the adventitia) and produces the more common fusiform shape (bulging or ballooning on all sides of the aorta), or a saccular shape (which bulges or balloons on only one side of the aorta), while a pseudoaneurysm involves only an enlargement of the outer wall of the blood vessel.

Figure 16. Thoracic Aortic Aneurysm Types



Pathogenesis

The aorta is considered an "elastic artery," meaning that it contains a series of fenestrated membranes composed of elastic sheaths within the media layer of the blood vessel wall. Elastin (providing recoil capacity) and collagen (providing tensile strength) are also present in differing amounts and in different cell structures in the

intima and adventitia. Lamellar units, which provide the structural framework for the media, serve to maintain the forward flow of blood during diastole and to aid in systole through expansion of the lamellae diameter.

Histologic examination of the aorta has revealed fragmentation, retrogression, and loss of elastic fibers, which is referred to as "medial degenerative disease." In advanced medial degenerative disease, smooth muscle cells are also lost. While no unified concept of the pathogenesis of TAAs has emerged, it has been hypothesized that degradation of the elastic fibers and smooth muscle tissue, and the loss of elastin and concomitant deterioration of structural integrity to the adventitia (which is responsible for maintenance of the maximal aortic outer diameter), combine to create a pathologic dilation of the blood vessel.(96) Atherosclerosis is frequently characterized in connection with the appearance of aortic dilation/aortic aneurysm. However, there is little support for the notion that it is the sole cause of TAA development. As with AAAs, the development of TAAs is likely to be multifactorial, including genetic predisposition, acquired biochemical alterations in the aortic wall related to aging, infection, and hemodynamic mechanical factors.

Incidence and Prevalence

It is believed that TAA currently affects approximately 21,000 individuals per year in the United States, with an overall incidence rate of TAA at 10.4 in 100,000 people per year.(170) Given the generally asymptomatic nature of the disorder, however, it is suspected that this number is an underestimate. According to Bickerstaff et al., the incidence of aortic aneurysm is approximately 5.9 per 100,000 person years.(171) A 1995 study by Johansson et al. specifically designed to obtain TAA rupture rates found that the mortality rate of the event in question was high (total mortality rate in 1989: 97%), with equal numbers of men and women affected.(172) Although autopsy findings vary, aneurysm prevalence in people over age 65 is estimated at 3% to 4%.(173) The five-year survival rate for untreated chronic TAA has been estimated at between 13% and 39%.

The years 1980 through 1994 saw a three-fold increase in incidence rates when compared to incidence rates for 1951 through 1980. The latter incidence rates are generally attributed to an aging population combined with improvements in diagnostic imaging methods that allow for the detection of smaller aneurysms.(170)

Mean age at diagnosis of an aortic aneurysm ranges between 59 and 69 years, with males exceeding females with a ratio of 2:1 to 4:1.(96)

Signs and Symptoms

Approximately 75% of TAAs are asymptomatic until rupture occurs. Depending on the location and size of the aneurysm, some individuals may present with symptoms such as diastolic murmur; pain in the jaw, neck, and upper back; chest or back pain; and coughing, hoarseness, or difficulty breathing or swallowing. Rare symptoms include hemoptysis. Symptoms associated with aortic rupture and subsequent blood loss include intense back and/or chest pain and signs of shock such as shaking, dizziness, fainting, sweating, rapid heartbeat, and sudden weakness (Table 42).

Table 42. Specific Signs and Symptoms of TAA

Aneurysm Location and Type	Signs and Symptoms
Ascending aortic aneurysms (causing dilation and leakage of the aortic valve)	Shortness of breath Heart failure (should leakage be severe) Dull pain underneath the breastbone or radiating to the upper back
Aortic arch aneurysms	Upper chest and back pain Difficulty swallowing and hoarseness due to compression of both the esophagus and the airway
Descending thoracic aneurysms	Back pain

Detection, Diagnosis, and Screening

Because approximately 75% of TAAs are asymptomatic, they are generally detected incidentally during routine clinical examination, or when a patient is undergoing a chest x-ray, echocardiogram, or CT chest scan for a reason other than TAA diagnosis.(96)[17] The most common imaging devices used in the diagnosis of TAAs include chest x-ray and CTA scan, with MRA (magnetic resonance angiography, a gadolinium-enhanced MRI) used to document the extent and size of the aneurysm. Other diagnostic imaging technologies include catheter-based angiography, transesophageal echocardiography and intravascular ultrasound.

Screening for TAAs has mainly focused on Familial Thoracic Aortic Aneurysm Syndrome, which is the family history of a development of TAAs not associated with an overt connective-tissue disorder such as Marfan syndrome or Ehlers-Danlos syndrome. Coady et al. found that some 19% of all individuals who experienced a TAA had relatives who had also experienced a TAA, with the age at presentation being significantly younger than those with sporadic aneurysm.(96) Tseng has noted that 15% of first-degree relatives of people who have had an aneurysm have also had an aneurysm.(173)

[17] Concomitant medical conditions associated with aortic aneurysm diagnosis include hypertension, coronary artery disease, COPD, and congestive heart failure.[Coady]

Genetically, there is some suggestion of an autosomal-dominant mode of inheritance, with mutations on 3p24.2-25 associated with both isolated and familial TAAs, and mutations on 5q13-14 and 11q23.2-q24 also linked to the development of TAAs. It is conjectured that having a TAA is a polygenic condition, with genetic screening currently not a possible detection option.(174)

Consequences of TAA Rupture

Rupture of an abdominal or thoracic aneurysm (and subsequent catastrophic hemorrhage) is the 13th leading cause of mortality in the United States, accounting for nearly 15,000 deaths annually. It has been estimated that between 20% and 30% of individuals with a ruptured TAA who arrive at hospital-alive survive the experience (Table 43). Surgery for a ruptured TAA carries a 25% to 50% mortality; elective surgery for a ballooning TAA carries a 5% to 8% risk of mortality. The mean rate of rupture or dissection is approximately 2% per year for aneurysms sized <5.0 cm, 3% for aneurysms sized 5.0 to 5.9 cm, and 6.9% for aneurysms sized 6.0 cm in diameter or greater.(173) The five-year survival rate of individuals with an *untreated* chronic TAA has been estimated at between 13% and 39%.(95) Consequences of aortic rupture or dissection other than mortality include paraplegia and paraparesis following aortic aneurysm repair, with an overall incidence rate for both of approximately 12% (immediate paraplegia 5.3%, delayed paraplegia 1.3%, immediate paraparesis 4.0%, and delayed paraparesis 1.3%).(175)

Table 43. Survival Time from Onset of Symptoms to Death in 135 Patients with Thoracic Aortic Rupture (Johansson et al. 1995)(172)

Survival Time	Number	% Alive
>6 hours	74	54%
7-24 hours	30	22%
>24 hours	32	24%
Total	135	100%

Established Treatment Options for Individuals with a TAA

There are a variety of potential treatment options for individuals with TAA; each of these options is dependent on the type of aneurysm, its size, and location, as well as the overall health of the individual involved.(101,176) None of these options provide a cure for an aneurysm, and in general, most aneurysms will need to be surgically repaired. The most common approaches to aneurysm treatment include the following:

Medication

Individuals with small asymptomatic aneurysms may receive medication such as antihypertensives to decrease blood pressure in the aorta and potentially slow the rate of aneurysm growth.(101)

Surgery

Large aneurysms present a dilemma in which the risks of the aneurysm rupturing must be weighed against the risks of performing surgery to correct the defect. For TAA, surgery is often indicated when an ascending aortic aneurysm or aortic arch aneurysm reaches a minimum diameter of 5 cm to 5.5 cm. Aneurysms of the descending aorta usually are allowed to reach a diameter of 6 cm before surgery is considered. Circumstances such as rapid aneurysm growth or comorbidities such as Marfan syndrome will require adjustments to decisions regarding when to operate on an aneurysm.

As opposed to AAA, in which there is a choice of open chest or endovascular surgery (depending on the aneurysm size, location, etc.) TAA repair involves open-chest surgery.(101,177) For aneurysms located close to the aortic valve or aortic arch, the incision and operation are located in the front of the chest. Surgery involving the aorta above the diaphragm usually requires the use of a cardiopulmonary bypass and cooling of the body temperature to stop blood flow (circulatory arrest) and allow repairs to take place. Once the repair is completed, the circulatory arrest is reversed. In cases where the aortic root has been damaged and requires repair or replacement, surgeons may choose from techniques such as native valve-sparing techniques and reconstruction with biological valves such as stentless xenographs and composite root replacement with a mechanical-valved conduit. Aneurysms located in the descending thoracic aorta or the thoracic-abdominal region are repaired through an incision located in the left side of the chest. Elefteriades noted that the current risks of death for aortic surgery were 2.5% for the ascending and arch of the aorta, and 8% for the descending and thoracoabdominal aortas.(178) Due to the mortality risk associated with TAA surgery, the choice of procedure is influenced not only by the location and size of the aneurysm, but by the age of the patient, his/her anticipated survival time, the underlying aortic pathology, considerations regarding the anatomical involvement of other structures such as the valve leaflets, sinuses, and annulus, and physician experience with a specific surgical technique.(176) The treatment of TAA by endovascular stent graft repair is currently considered experimental, and thus is rarely considered as an alternative to open surgical repair.(179,180)

Watchful Waiting

Individuals with small asymptomatic aneurysms may undergo regular CT scan, MRI, ultrasound, or echocardiogram every 6 to 12 months to monitor the amount and rate of aneurysm growth. This allows for the optimum surgical treatment of the aneurysm.(178)

Guidelines for Treatment of TAAs

The most current guidelines for treatment of TAA were published in 1995 by the Ad Hoc Committee for Cardiothoracic Surgical Practice Guidelines. The publication *Practice guidelines in cardiothoracic surgery: thoracic aortic disease* detailed the necessary information for managing thoracic aneurysms, such as diagnosis, indication and confirmation of indication, contraindications, and actions prior to, during, and following surgical procedures and outcome. TAA sites covered by the guidelines include the descending transverse arch, ascending transverse arch, and aortic aneurysm of unspecified site (thoracoabdominal aortic aneurysm).(181-183)

Identification of Evidence Base

The purpose of this section is to systematically review the data pertaining to the risk factors associated with TAA rupture with the aim of informing FMCSA about the factors that have been shown to predict which individuals with a TAA are most at risk for sudden incapacitation due to TAA rupture. In attempting to address this issue we searched for studies of any design that attempted to identify risk factors for TAA rupture. These studies included case-control trials, case series, controlled trials in which a group of individuals with a TAA did not receive treatment, and natural history studies. Our decision to include studies of any design was motivated by the fact that we were aware that data on the risk factors for TAA rupture would be rare. The statement by Brewster regarding AAA, "Accurate data on rupture risk are likely the least precise of the several variables which need to be assessed in the decision-making process. This is due to the fact that in the past three decades few patients have been followed without intervention; hence, the true natural history of untreated AAA remains somewhat poorly defined",(135) is equally applicable to the evidence for a TAA.

The identification of the evidence user in this section of the evidence report is presented in Figure 17. Our searches[18] identified a total of 29 articles that appeared

[18] See Appendix A for search strategies.

relevant. Following application of the retrieval criteria for this question, 29 full-length articles were retrieved and read in full. Seven of these 29 retrieved articles were found to meet our criteria for inclusion[19] (Table 44).

Table D-2 of Appendix D lists the 22 articles that were retrieved but then excluded and provides the reason for their exclusion. Detailed information pertinent to this section that has been extracted from the included studies is presented in the Study Summary Tables that can be found in Appendix G.

Figure 17. Development of Evidence Base for Key Question 2

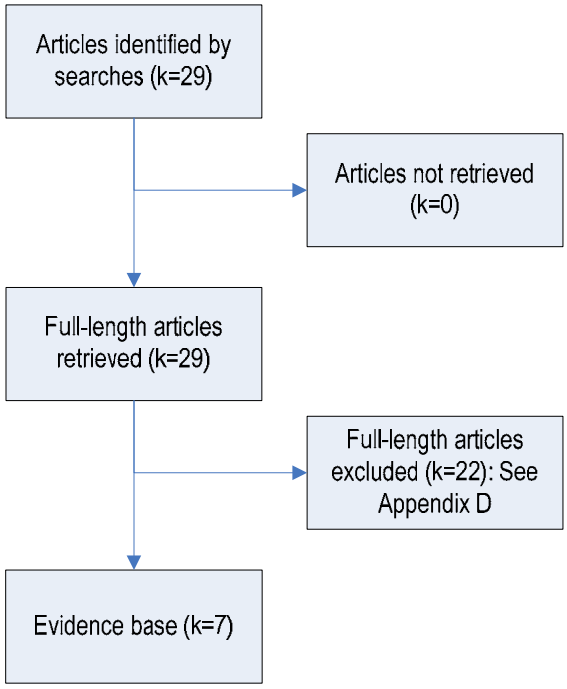


Table 44. Evidence Base for TAA

Primary Reference	Year	Study Location	Country
Davies et al.(184)	2006	Connecticut	USA
Elefteriades JA(178)	2002	Connecticut	USA
Davies et al.(185)	2002	Connecticut	USA

[19] See Appendix C for inclusion criteria.

Primary Reference	Year	Study Location	Country
Coady et al.(96)	1999	Connecticut	USA
Griepp et al.(167)	1999	New York	USA
Clouse et al.(170)	1998	Minnesota	USA
Juvonen et al.(186)	1997	New York	USA

Evidence Base

This subsection provides a brief description of the key attributes of the seven studies that met the inclusion criteria for this key question. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Detailed information pertinent to this section that has been extracted from included studies is presented in the Study Summary Tables that can be found in Appendix G.

The primary characteristics of the seven included studies that address Key Question 2 are presented in Table 45. Four of the studies were retrospective; the remaining three were prospective. Most of the articles ascertained the rate of TAA rupture in a cohort of individuals and attempted to identify risk factors associated with a rupture event.

Although the mortality rate associated with rupture of a TAA is high, not all patients have the same risk of rupture. According to Isselbacher, the etiology and location of an aneurysm may affect its risk of rupture. In addition, the increasing use of imaging systems, aneurysm sizing, and resulting use of surgery on aneurysms—which pose a significant risk of rupture—have made actual ruptures a rarer event than was noted in the past.(101)

Rupture risk depends on a number of factors, the most important and common of which appears to be aneurysm diameter.(96,185,187,188) Other factors that may also influence the likelihood of rupture include the type of aneurysm (saccular versus fusiform) and presence of a connective tissue comorbidity such as Marfan syndrome.(189) Factors that may influence aneurysm *growth* in a maximally dilated aortic segment include thrombus, transient ischemic attack (TIA)/stroke, smoking, peripheral vascular disease, and COPD.(95)

Table 45. Key Study Design Characteristics of Studies that Address Key Question 2 – TAA

Reference	Year	Size	Study Design	Prospective or Retrospective	Potential Risk Factors Assessed	Were multivariable risk models considered?
Davies et al.(184)	2006	805	Cohort	Retrospective	Aortic diameter index Aneurysm location Gender History of AAA	Multivariate logistic regression Kaplan-Meier product limit estimates
Elefteriades JA(178)	2002	1600	Cohort	Retrospective	Aortic size	Not disclosed
Davies et al.(185)	2002	721	Cohort	Retrospective	Initial aortic diameter Gender Marfan syndrome Aneurysm location AAA	Chi-square test Mantel-Haenszel Chi-square test Wilcoxon test Logistic regression Kaplan-Meier life table estimates with log-rank test Cox regression model
Coady et al.(96)	1999	370	Cohort	Prospective	Aortic diameter Aneurysm location Age Gender	Logistic regression
Griepp et al.(167)	1999	165	Cohort	Prospective	Age COPD Uncharacteristic chronic pain Hypertension Renal failure	Not disclosed
Clouse et al.(170)	1998	133	Cohort	Retrospective	Gender Age Hypertension Smoking Hyperlipidemia Family history of aneurysm COPD Aneurysm diameter Symptoms at diagnosis Subsequent dissection Saccular	Kaplan-Meier Cox proportional hazards model
Juvonen et al.(186)	1997	114	Cohort	Prospective	Age Pain COPD Aortic diameter Gender History of hypertension Smoking Diabetes mellitus	Logistic regression

AAA Abdominal aortic aneurysm.
COPD Chronic obstructive pulmonary disease.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 1 are presented in Table 46. The included studies consisted entirely of cohort studies. This assessment found that the quality of the included studies was not high. All seven of the included studies were graded as low quality. Cohort studies can be either

prospective or retrospective, and are susceptible to bias through differences in patient selection, follow-up, and measurement bias (particularly in how measurements are taken and how the data is analyzed). Therefore, a well-designed cohort study cannot be graded as high quality. Other factors that differentiated moderate- from low-quality studies included poor reporting, failure to adjust for exposure differences (such as the length of time each study participant had had an aneurysm), and questions regarding whether certain studies had achieved the statistical power necessary to investigate a rare event such as aneurysm rupture.(152)

Table 46. Quality of Studies of TAA Rupture Risk

Reference	Year	Quality Scale Used	Quality Score	Quality
Davies et al.(184)	2006	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Elefteriades JA(178)	2002	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Davies et al.(185)	2002	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Coady et al.(96)	1999	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
Griepp et al.(167)	1999	Newcastle-Ottawa Quality Assessment Scale	4.75	Low
Clouse et al.(170)	1998	Newcastle-Ottawa Quality Assessment Scale	7.75	Low
Juvonen et al.(186)	1997	Newcastle-Ottawa Quality Assessment Scale	6.75	Low
		Overall Quality	6.60	Low

Generalizability of Evidence to Target Population

None of the studies featured in this section of the cardiovascular report specifically included information about the occupations of the participants, making it impossible to generalize on the basis of employment. As acknowledged in the *Study Design* section, the heterogeneity of the populations represented in the included studies also precludes us from making a definitive statement about the generalizability of the evidence to the target population (CMV drivers).

Findings

As outlined in the previous section on study design, due to heterogeneity in the data as a result of numerous factors (use of very different populations, lack of standardization, referral bias, and selection bias), the relationship of risk factors to aortic rupture could not be quantified in this report.

As demonstrated by the data presented in Table 47, TAA rupture risk appears to be related to the most important and consistently identified independent risk factor for TAA rupture: aneurysm size. A single study(186) identified three other risk factors: age, COPD, and presence of uncharacteristic chronic pain.

Table 47. Results of Studies on Rupture of a TAA

Study	Year	Size	Model	Univariate	Multivariate
Davies et al.(184)	2006	805	Multivariate logistic regression Kaplan-Meier product limit estimates	Significant variables: • Initial aortic diameter • Increasing aortic diameter; 4.25 cm/m^2 – 4.99 cm/m^2 associated with OR 7.9577 • Aneurysm location in descending or thoracoabdominal aorta • History of AAA	Significant variables: • Increasing aortic diameter (4.25 cm/m^2 – 4.99 cm/m^2 associated with OR 13.765, CI 3.048 – 62.171) • Aortic diameter of 5.00 cm/m^2 or greater (OR 7.577, CI 1.167 – 48.932) • Aneurysms located in the descending or thoracoabdominal aorta (OR 2.581, CI 1.012 – 6.584) Proportional hazards regression model for rupture alone demonstrated: • Hazard function for rupture is more than 11x worse for patients with aortic size indexes (ASIs) above 4.25 cm/m^2 than for those with an ASI or 2.00 cm/m^2 – 2.74 cm/m^2 • Descending and thoracoabdominal aneurysms associated with increased risk of rupture (OR 2.380,CI 1.321 – 4.290) Incidence of rupture as a function of time (5 year event-free survival) Significant variables: • Initial aortic diameter (larger predicted worse event survival) • Descending or thoracoabdominal aortic location of aneurysm had higher rupture rates • History of AAA had higher rupture rates
Elefteriades JA(178)	2002	1600	Not disclosed	Significant variable: • Aortic diameter	Complications based on aortic diameter (yearly risk of rupture): • 3.5 cm: 0.0% • 4 cm: 0.3% • 5 cm: 1.7% • >6 cm: 3.6%
Davies et al.(185)	2002	570	Chi-square test Mantel-Haenszel Chi-Square test Wilcoxon test Logistic regression Kaplan-Meier life table estimates with log-rank test Cox regression model	Significant variables: • Initial aortic diameter of 6 cm (OR 3.762) • Gender (male, protective from rupture) (OR 0.365) • Aneurysm location (descending or thoracoabdominal regions) (OR 3.243) • AAA (OR 4.663)	Significant variables: • Aortic diameter ≥6 cm (OR 5.227 CI 1.855 – 14.727) • Gender (male, protective from rupture) (OR 0.340 CI 0.141 – 0.819) • Marfan syndrome (OR 3.668 CI 1.096 – 12.278) Incidence of rupture as a function of time Significant variables: • Aortic diameter (5.0 – 5.9 cm) (11.032 CI 1.227 – 99.156) • Aortic diameter (≥6 cm) (OR 26.976 CI 3.229 – 225.334)
Coady et al.(96)	1999	370	Logistic regression	NR	Significant variables: Initial aneurysm diameter: • 5.0 – 5.9 cm (OR 2.08 CI 0.26 – 3.69) • 6.0 – 6.9 cm (OR 4.27 CI 1.63 – 11.15) • ≥7 cm (OR 2.90 CI 1.01 – 8.33)

Study	Year	Size	Model	Univariate	Multivariate
Griepp et al.(167)	1999	165	Not disclosed	NR	Significant variables Non-dimensional: • Age • COPD • Pain (uncharacteristic continued) Dimensional: • Diameter • Growth rate
Clouse et al.(170)	1998	133	Kaplan-Meier Cox proportional hazards model	Significant variables: • Development of dissection in aneurysm • Female gender • Symptoms at diagnosis • Age at diagnosis	Significant variables: • Female gender • Symptoms at diagnosis
Juvonen et al.(186)	1997	114	Logistic Regression	NR	Significant variables: • Maximal diameter in the descending (Relative Rate: 1.9) and abdominal aorta (Relative Rate: 1.50) • Age (Relative Rate: 2.6) • Pain (presence of uncharacteristic) (Relative Rate: 2.3) • History of COPD (Relative Rate: 3.6)

AAA Abdominal aortic aneurysm.
ASI Aortic size index.
CI Confidence interval.
COPD Chronic obstructive pulmonary disease.
NR Not reported.
OR Odds ratio.

Table 48. Independent Risk Factors for Rupture of a TAA

Study	Year	Risk Factors															
		Aortic Diameter	Location	Gender	Family History of Aneurysm	Hyperlipidemia	Symptoms at Diagnosis	Renal Failure	Age	Aortic Diameter	Pain	COPD	Presence of AAA	Presence of Dissection	Hypertension	Marfan Syndrome	Diabetes
Davies et al.(184)	2006	✓															
Elefteriades JA(178)	2002	✓															
Davies et al.(185)	2002	✓															
Coady et al.(96)	1999	✓															
Griepp et al.(167)	1999	✓															
Clouse et al.(170)	1998	✓															
Juvonen et al.(186)	1997	✓							✓		✓	✓					

✓ risk factor proved significant
AAA Abdominal aortic aneurysm.

COPD Chronic obstructive pulmonary disease.

The most important risk factor for TAA rupture is aneurysm diameter. Applying La Place's law to aortic aneurysm, it is likely that aortic expansion accelerates as the diameter of the aneurysm increases, making rupture more likely.(187) Based on a natural history study of yearly rupture or dissection rates for TAAs, Davies et al.(185) proposed that the risk of rupture alone is near zero for aneurysms <5.0 cm, 1.7% for aneurysms with a diameter of 5.0 to 5.9 cm, and 3.6% for aneurysms with a diameter of 6.0 cm or greater. Risk of rupture, dissection, or death from all causes is 6.5% at aneurysm with a diameter of 5.0 to 5.9 cm and 14.1% per year for aneurysms of 6.0 cm or greater.

The rate of descending thoracic aneurysm enlargement (DeBakey type III, the most common site of thoracic aortic enlargement) is estimated to be a 0.32 cm per year increase in diameter and a 53 ml per year increase in volume. A large (>5 cm) diameter at diagnosis will be the best predictor of a high expansion rate. Rizzo et al. (1997) reported different growth rates, with mean estimated growth rate of aortic expansion at 0.1 cm per year, with >6 cm aneurysms growing more rapidly than aneurysms <6 cm, with aneurysms in the descending thoracic or thoraco-abdominal aorta growing more rapidly than aneurysms growing in the ascending aorta or aortic arch (DeBakey type I and II), and aneurysms in males growing at a more rapid pace than aneurysms in females.(190) In concordance with Rizzo's conclusions, Elefteriades 2002 study(178) found that TAAs grow (on average, combining males and females) at a rate of approximately 0.10 cm per year, with expansion rates of 0.07 cm per year for ascending and 0.19 cm per year for descending segments of the thoracic aorta.

Much of the research devoted to TAAs has revolved around developing guidelines for surgical intervention (i.e., finding the so-called "hinge point" where aneurysm diameter has reached a critical juncture which justifies the risk of surgery to prevent dissection or rupture). According to Dapunt et al.,(187) small aneurysms (<5 cm) that are not undergoing rapid expansion carry a low rupture risk and can be part of a "watchful waiting" program of observation over 6 to 12 month intervals. Elefteriades(178) found that the critical dimensions for rupture or dissection were 6.0 cm for the ascending aorta and 7.0 cm for the descending aorta, with patients who had reached these dimensions having a likelihood of rupture or dissection estimated at 31% for the ascending segment and 43% for the descending aortic segment. Those individuals who reached 6 cm maximum diameter of the aorta had estimated yearly rates for the following events: rupture 3.6%; dissection 3.7%; death 10.8%; and rupture, dissection, or death 14.1% (Table 49).

Risk of death associated with surgery for a TAA was 2.5% for the ascending aorta segment and aortic arch, and 8% for the descending and thoracoabdominal aortic segments. Coady et al. (1997) considered a thoracic aortic diameter of 6 cm to be the "hinge point" beyond which the probability of rupture increased by 30%.(188)

Table 49. Risk Stratification Derived from TAA Evidence Base

Study	Year	Size	Risk Stratification by Abdominal Aortic Aneurysm Diameter
Davies et al.(184)	2006	805	OR risk of rupture by year <2.00 cm/m^{2}: 1.570 2.75 – 3.49 cm/m^{2}: 2.013 3.50 – 4.24 cm/m^{2}: : 1.113 4.25 – 4.99 cm/m^{2}: : 3.659 ≥5 cm/m^{2}: : 5.152
Elefteriades JA(178)	2002	1600	Risk of adverse event per year at aneurysm diameter >6 cm: Rupture: 3.6% Dissection: 3.7% Death: 10.8% Rupture, dissection, or death: 14.1%
Davies et al.(185)	2002	721	OR of risk of rupture by year 5.0 – 5.9 cm: 1.303 ≥6.0 cm: 3.762
Coady et al.(96)	1999	370	OR of risk of rupture by year 3.5 – 3.9 cm: 0.97 5.0 – 5.9 cm: 2.08 ≥6.0 cm: 4.27 ≥7 cm: 2.90
Griepp et al.(167)	1999	165	Increased odds of rupture: COPD: 3.6 Age: 2.6 Pain: 2.3
Clouse et al.(170)	1998	133	5-years cumulative risk of rupture related to TAA diameter: >4 cm: 0% 4 – 5.9 cm: 16% ≥6 cm: 31% 5-years rupture risk related to anatomic extent of TAA Ascending: 9% Descending: 26% Both ascending and descending: 29%
Juvonen et al.(186)	1997	114	Relative rate (independent risk factors for rupture of descending thoracic and thoracoabdominal aneurysms) Age: RR 2.6 (for each decade of age the RR increases by 2.6) Pain: 2.3 COPD: 3.6 Descending aortic diameter: 1.9 (for each cm of descending thoracic aortic artery) Thoracoabdominal aortic diameter: 1.50 (for each cm of thoracoabdominal aortic artery)

COPD Chronic obstructive pulmonary disease.
OR Odds ratio.
RR Rate ratio.
TAA Thoracic aortic aneurysm.

Statistics and Optimal Clinical Care of TAA

Aneurysm of the thoracic aorta is a potentially life-threatening condition, both from the possibility of aortic dissection, rupture, and death, and the perspective of adverse sequelae to surgical intervention. The need for an accurate method to assess complication risk (Table 50) and create appropriate treatment protocols is important for the clinician in providing optimal care for the individual with an aortic aneurysm.(166) To this end, efforts have been concentrated on finding sound statistical methods of calculating the expansion rate of an aneurysm and the risk of aortic rupture. This will be easy for the clinician to use and will provide accurate estimates of these crucial details in aortic aneurysm care. The currently available calculations are featured in the following sections.

Table 50. Yearly Risk of Complications Based on TAA Size

	Aortic Size			
Yearly Risk of:	**>3.5 cm**	**>4 cm**	**>5.0 cm**	**>6.0 cm**
Rupture	0.0%	0.3%	1.7%	3.6%
Dissection	2.2%	1.5%	2.5%	3.7%
Death	5.9%	4.6%	4.8%	10.8%
Any of the above	7.2%	5.3%	6.5%	14.1%

* Adapted From Elefteriades(178)

Calculation of Expansion Rate of TAA

The linear expansion rate [ER] of a TAA can be calculated in the following manner:

ER = [(last diameter) – (initial diameter) (mm)] / (interval) (years)

while the expansion rate [%ER] of a TAA is calculated with the following equation(95):

%ER = ER / initial diameter x 100

Calculation of Risk of a Thoracic Aortic Rupture

The risk of rupture in any year can be calculated for any one patient using the following equation developed by Juvonen et al., where λ = *rate of rupture*.

$$Ln\lambda = -21.055 + 0.093 \text{ (age) and } 0.841 \text{ (pain) } + 18.22 \text{ (COPD) } + 0.643 \text{ (descending diameter in cm) } + 0.405 \text{ (abdominal diameter in cm)}$$

Pain and COPD = 1 if present and 0 if absent or not reported, and age refers to the time of the most recent scan.

Probability of rupture within 1 year is $1 - e^{\lambda(365)}$

Summary of Findings

The most commonly identified risk factor for TAA rupture is aneurysm size (Strength of Evidence: Acceptable).

- **Due to the fact that there were a number of methodologic problems involving heterogeneity of the populations studied, biases, statistical power issues, and lack of standardization regarding aneurysm measurement and reporting, we did not attempt to determine a quantitative model describing the risk of rupture for an aortic aneurysm or TAA.**

  Seven (Total N = 3,908) low-quality studies assessed the potential risk factors for rupture of a TAA. These seven studies demonstrated that aneurysm size was the most important risk factor associated with aneurysm rupture (n = 7). Other risk factors identified for thoracic aortic rupture included age (n = 1), presence of uncharacteristic, chronic pain (n = 1), and COPD (n = 1).

Key Question 3: Is implantation of a pacemaker effective in preventing vasovagal syncope recurrence?

Background

FMCSA's current guidelines state that individuals with vasovagal (neurocardiogenic) syncope have an "…excellent long-term survival prognosis but there is risk for syncope that may be due to cardioinhibitory (slowing heart rate) or vasodepressor (drop in blood pressure) components, or both. Pacemaker will affect only cardioinhibitory component, but will lessen effect of vasodepressor component."(26) The guidelines for medical examiners note that individuals with recurrent vasovagal syncope should not be allowed to drive if they are symptomatic. Individuals with an implanted pacemaker may be certified to drive a commercial vehicle three months after implantation provided that 1) no syncopal recurrences have occurred during that time; and 2) The device has been certified as functioning correctly by a "pacemaker center."(26)

Since the publication of these guidelines, new evidence from two double blind RCTs has been published that warrants the reevaluation of the evidence pertaining to the effectiveness of pacemakers in the treatment of recurrent vasovagal syncope. The

purpose of this section is to provide FMCSA with a synthesis of the best and most current available evidence on the effectiveness of implanted pacemakers when used to treat individuals with recurrent vasovagal syncope.

Vasovagal Syncope

Recurrent vasovagal syncope (or neurocardiogenic syncope) is a common non-life-threatening disorder in which an individual losses consciousness (typically while sitting or standing) following exposure to a "trigger." Though not life threatening in and of itself, vasovagal syncope is a safety concern because subsequent sudden incapacitation may result in crashes. In most (but not all) cases, affected individuals may experience a prodrome that might include lightheadedness, nausea, sweating, ringing in the ears, and visual disturbances, with these symptoms lasting for at least a few seconds before consciousness is lost.

Typical triggers for vasovagal syncope include the following:

- Prolonged standing
- Any painful or unpleasant stimuli, such as:
    - Prolonged exposure to heat
    - Emotional extremes
    - Hunger
    - Nausea or vomiting
    - Urination ("micturition syncope") or defecation
    - Swallowing ("deglutition syncope")

Regardless of the trigger, the mechanisms leading to the syncopal event are similar. The nucleus tractus solitarius of the brainstem is activated directly or indirectly by the triggering stimulus, resulting in simultaneous enhancement of parasympathetic nervous system (vagal) tone and withdrawal of sympathetic nervous system tone. This results in a spectrum of hemodynamic responses in individuals with syncope, the primary hemodynamic responses consist of a combination of the cardioinhibitory response and the vasodepressor response. The cardioinhibitory response is characterized by bradycardia (60 beats per minute or less)(24) which in turn leads to a drop in blood pressure severe enough to cause loss of consciousness. The vasodepressor response is characterized by a drop in blood pressure resulting from vasodilation, which is thought to occur as a consequence of the withdrawal of sympathetic nervous system tone.

Typical treatments for vasovagal syncope focus primarily on trigger avoidance, measures aimed at restoring blood flow to the brain during an impending episode, and interruption or prevention of the pathophysiologic mechanism described above. Before known triggering events, the patient may increase consumption of salt and fluids to increase blood volume. In addition, the following pharmacotherapeutic options are available, although their efficacy is in question:

- Beta blockers (β-adrenergic antagonists) are the most common medication given. They work by lessening myocardial contractility, the sudden increase in the force with which the heart pumps.
- Other medications which may be effective include fludrocortisones, midodrin, serotonin reuptake inhibitors such as paroxetine or sertraline, and desipramine.

In the mid 1990's it was suggested that pacemakers may help individuals with recurrent vasovagal syncope.

Pacemakers

Pacemakers are electronic devices designed to detect and correct bradycardia (cardiac arrhythmias characterized by abnormally slow heartbeats). Bradycardia can produce symptoms including fatigue, weakness, light-headedness, dizziness, and fainting. Untreated bradycardia may lead to death.

Pacemakers have two major parts (the generator and the leads) that function to regulate the timing of the heartbeat. The generator is a tiny, sealed computer with a battery housed in a titanium container. The lead is a flexible, insulated electrical wire that connects the generator to one of the heart's chambers. The tip of the lead contains an electrode that delivers the necessary electrical impulses to the heart (pacing). Single-chamber pacemakers operate with the lead placed in either the right ventricle or the right atrium, depending on which type of pacing is indicated. Dual-chamber pacemakers use two leads: one placed in the right atrium and the other placed in the right ventricle.

Dual-chamber pacemakers can be programmed to pace only one chamber (either the atrium or the ventricle) or two chambers.(191-193) It is often referred to as physiologic pacing because, unlike single-chamber ventricular pacing, dual-chamber pacing can restore atrioventricular (AV) synchrony. Recent studies have suggested that AV synchrony is only a single component of a physiologically normal heartbeat. However, ventricular-ventricular synchrony plays a part in the production of the normal heartbeat, and there is some evidence that the benefits of AV synchrony can be

mitigated by the presence of ventricular dyssynchrony.(191-193) Ventricular dyssynchrony may occur with any pacing mode that leads to frequent pacing of the right ventricle, and while single-chamber atrial pacing avoids the problem of ventricular dyssynchrony, it cannot be used in patients with advanced AV block.(194)

The focus on physiologic pacing has led to the development of sensor-driven, rate-modulated pacemakers that detect the level of exercise or metabolic need and modulate the heart rate accordingly (chronotropic competence). In the year 2000, roughly 97% of pacemakers implanted in the United States had rate modulation as a programmable option to provide chronotropic competence.(191)

Implanting permanent pacemakers involves minimally invasive surgery, which is performed under local anesthesia and usually takes between one to two hours. After creating a small incision (approximately three inches in length), most commonly in the left side of the chest below the collarbone, the surgeon fashions a "pocket" in the shoulder area either above the pectoral muscle in subcutaneous tissue or below the pectoral muscle. The generator is placed in the pocket. Leads are inserted through a vein near the site of the pocket, advanced into the heart using fluoroscopic guidance, and attached to the generator, after which the incision is closed. The pacemaker is then programmed to a specific pacing mode using a handheld device that signals the generator through the skin.(195) The procedure can be performed on an inpatient or outpatient population, allowing some patients to leave the hospital later the same day, while older or less healthy patients may stay overnight.

In the absence of complications, the patient can typically resume a normal lifestyle within two to three weeks, with regularly scheduled pacemaker checkups usually scheduled by the treating physician on a 6- to 12-month basis.

Rationale for Pacemaker Use in Individuals with Vasovagal Syncope

Tilt-table studies found that some forms of vasovagal syncope involve both a cardioinhibitory as well as a vasodilatory component. In addition, up to 60% of individuals with head-up tilt-induced vasovagal syncope have bradycardia. Thus, it has been hypothesized that pacemakers may be effective in preventing, or at least lessening, the degree of symptoms experienced during a vasovagal episode by increasing heart rate.

The pacemaker first senses the onset of an event and then increases the heart rate above the normal resting heart rate (60 beats per minute) so that the heart is able to

overcome the transient blood pressure reduction that accompanies bradycardia. Pacemakers used to treat individuals with recurrent vasovagal syncope usually have one of three specialized sensing modes: rate smoothing, rate hysteresis, and rate-drop sensing. All three modes are designed to detect a relatively rapid fall in heart rate. Once the onset of a vasovagal event is detected, a rapid atrioventricular sequential pacing occurs at a rate of between 90 and 110 beats per minute. This rate is considered adequate enough to limit blood pressure loss and stop the onset of syncope.(196)

Early Evidence

Several uncontrolled studies evaluated the efficacy of pacemakers in preventing vasovagal syncope.(197-199) Patients enrolled in all of these studies experienced vasovagal syncope with bradycardia during a tilt-table testing. They all consistently found that cardiac pacing could effectively prevent vasovagal syncope.

Clinical Practice Guidelines for Treatment of Syncope

There are two current clinical practice guidelines extant for the treatment of syncope. The 2004 clinical practice guidelines from the Task Force on Syncope of the European Society of Cardiology titled, "Guidelines on Management (Diagnosis and Treatment) of Syncope"(200,201) state the following:

> *"Pacing for vasovagal syncope has been the subject of five major multicenter randomized controlled trials: three gave positive and two negative results. Putting together the results of the 5 trials, 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of not paced patients (p <0.001). However, all the studies have weaknesses and further follow-up studies addressing many of these limitations (particularly the pre-implant selection criteria of the patients who might benefit from pacemaker therapy) need to be completed before pacing can be considered an established therapy."*

The 2002 ACC/AHA/NASPE guideline update titled, "Implantation of Cardiac Pacemakers and Antiarrhythmia Devices"(202) asserts that:

> *"The role of permanent pacing in refractory neurocardiogenic syncope associated with significant bradycardia or asystole is controversial."*

The guideline update goes on to state:

"Approximately 25% of patients have a predominant vasodepressor reaction without significant bradycardia. An additional large percentage of patients will have a mixed vasodepressor/vasoinhibitory component of their symptoms. While one group of investigators have noted some benefit of pacing in these patients, another study using a pacing rate 20% higher than the resting heart rate demonstrated that pacing did not prevent syncope any better than pharmacotherapy.

Because most individuals with neurocardiogenic syncope have a slowing of heart rate after the fall in blood pressure, pacing may be ineffective in most patients. Dual-chamber pacing, carefully prescribed on the basis of tilt-table test results, may be effective in reducing symptoms if the patient has a significant cardioinhibitory component to the cause of their symptoms. Results from a randomized trial in highly symptomatic patients with bradycardia demonstrated that permanent pacing increased the time to first syncopal event. In another trial, the actuarial rate of recurrent syncope at 1 year was 18.5% for pacemaker patients and 59.7% for control patients. The specific modality of pacing under these circumstances is under active investigation. One study demonstrated that DDD pacing with rate-drop response function was more effective than beta-blockade in preventing recurrent syncope in highly symptomatic patients with vasovagal syncope and relative bradycardia during tilt-table testing."

Evidence Base Identification

In attempting to answer this question we searched for RCTs that evaluated the effectiveness and safety of dual-chamber pacemakers when used for the treatment of individuals with vasovagal syncope. The identification of the evidence base for Key Question 3 is summarized in Figure 18. Our searches[20] identified a total of 62 articles that appeared relevant to this key question. Following the application of a set of retrieval criteria for this question[21], 14 full-length articles were retrieved and read in full. Five of these 14 retrieved articles were found to meet the inclusion criteria[22] for Key Question 3

[20] See Appendix A for search strategies.

[21] See Appendix B for retrieval criteria.

[22] See Appendix C for inclusion criteria

(Table 18). Table D-3 of Appendix D lists the nine articles that were retrieved but then excluded and provides the reason for their exclusion.

Figure 18. Development of Evidence Base for Key Question 3

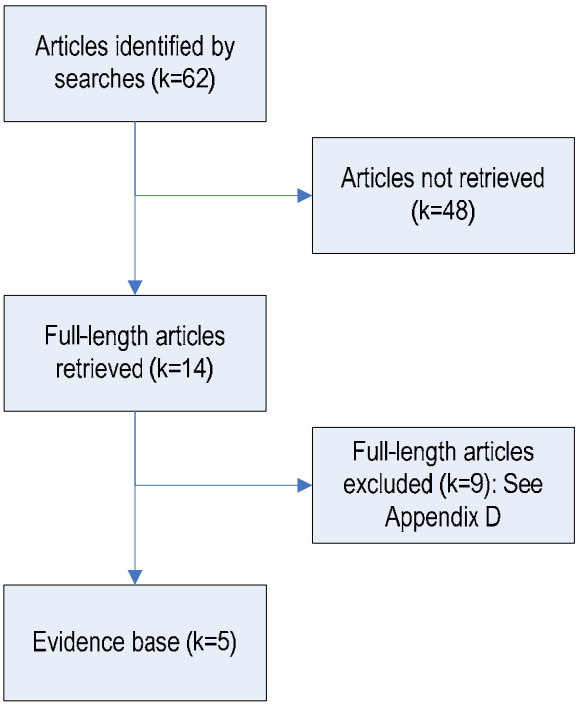


Table 51. Evidence Base for Key Question 3

Primary Reference	Year	Study Acronym (if applicable)	Secondary References	Study Location	Country
Raviele et al.(203)	2004	SYNPACE	Raviele et al.(204)	Multicenter (30 centers)	Italy
Connolly et al.(205)	2003	VPS II	Sheldon and Connolly(206)	Multicenter (15 centers)	Canada, Australia, the United States, and Colombia
Ammirati et al.(207)	2001	SYDIT	NA	Multicenter (14 centers)	Italy
Sutton et al.(208)	2000	VASIS	NA	Multicenter (18 centers)	Italy, Sweden, the United Kingdom, Poland, and Spain
Connolly et al.(209)	1999	VPS	Sheldon et al.(210)	Multicenter (14 centers)	Canada and the United States

NA Not applicable.

Evidence Base

This subsection provides a brief description of the key attributes of the five included studies that assessed the efficacy and safety of permanent dual-chamber pacemakers

in individuals with vasovagal syncope. Applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs will be addressed. Detailed information pertinent to this section that has been extracted from the included studies is presented in Study Summary Tables that can be found in Appendix G.

The key attributes of each of the five included studies that address Key Question 3 are presented in Table 52. As per the inclusion criteria for this question, all five studies were RCTs that compared the effectiveness of a dual-chamber pacemaker to standard medical treatment. The effectiveness of the pacemaker was compared with standard medical treatment in three studies(207-209) and with a "sham" in the remaining two studies.(203,205) In both of the latter studies, the sham was an identical dual-chamber pacemaker that was used in the treatment group; for the control group, however, the pacemaker was not activated.

Table 52. Key Study Design Characteristics (Pacemakers for Vasovagal Syncope)

Reference	Year	Design	Pacemaker device(s)	N =	Comparison Group	Follow-up time: months ±SD
Raviele et al.(203)	2004	Randomized Multicenter Double-Blind	Vitatron Clarity DR DDD-RDR Mode	29	Implanted pacemaker-switched off	Pacemaker: Median: 563 days Control: Median: 730 days
Connolly et al.(205)	2003	Randomized Multicenter Double-Blind	Medtronic Kappa DDD-RDR Mode	100	Implanted pacemaker-switched off	Up to 6 months
Ammirati et al.(207)	2001	Randomized Multicenter Open	Medtronic Thera-I, model 7960, DDD-RDR Mode	93	No pacemaker – standard medical therapy (all put on Atenol)	Mean: 35.4 months
Sutton et al.(208)	2000	Randomized Multicenter Open	Paragon III or Trilogy DC DDI-RH Mode	42	No pacemaker – standard medical therapy	Mean: 3.7 years SD: 2.2 years Range: 1 to 6.7 years
Connolly et al.(209)	1999	Randomized Multicenter Open	Medtronic-Model NR DDD-RDR Mode	54	No pacemaker – standard medical therapy	NR

NR Not reported.
RDR Rate-drop response.
RH Rate hysteresis.
SD Standard deviation.

Quality of Evidence Base

The results of our analysis of the overall quality of the evidence base for Key Question 3 are presented in Table 53. This assessment found that the quality of all of the included studies was in the moderate to high range. Two studies were graded as being high quality.(203,205) Three studies were graded as being moderate quality.(207-209)

Table 53. Quality of Evidence Base (Pacemakers for Vasovagal Syncope)

Reference	Year	Quality Scale Used	Quality Score	Quality
Raviele et al.(203)	2004	ECRI Quality Scale 1: Controlled Trials	High	9.6
Connolly et al.(205)	2003	ECRI Quality Scale 1: Controlled Trials	High	9.2
Ammirati et al.(207)	2001	ECRI Quality Scale 1: Controlled Trials	Moderate	8.3
Sutton et al.(208)	2000	ECRI Quality Scale 1: Controlled Trials	Moderate	8.8
Connolly et al.(209)	1999	ECRI Quality Scale 1: Controlled Trials	Moderate	7.0

Only two of the trials (both graded as high quality) were double-blind; both studies used a sham pacemaker that was turned off and neither the patient nor the physician collecting the outcome data was aware of whether the volunteer was assigned to the treatment or control arm of the study. Attrition rates were very low in all included studies and all utilized intent-to-treat principles.

Generalizability of Evidence to Target Population

The generalizability of the individuals enrolled in the five included studies to CMV drivers is unclear (Table 54). Patients enrolled in the five included RCTs experienced frequent episodes of vasovagal syncope that was refractory to other methods of treatment; they were tilt-table positive for bradycardia, and they were free from evidence of major CVD.

Table 54. Patient Population in Studies that Assess Key Question 3

	Raviele et al.(203)	Connolly et al.(205)	Ammirati et al.(207)	Sutton et al.(208)	Connolly et al.(209)
Year	2004	2003	2001	2000	1999
Inclusion Criteria	Frequently recurrent syncopes and positive head-up tilt testing with asystolic or mixed response, ≥6 syncopal events in the patients lifetime, last occurrence ≤6 months before enrollment; ≥1 recurrence within 12 months of positive head-up tilt testing, exclusion of any other cause of syncope after a complete work-up, age ≥18 years.	Age ≥19 years and if they had a typical history of recurrent vasovagal syncope with ≥6 episodes of syncope ever, or ≥3 episodes in the 2 years prior to enrollment. In addition, patients had to have a positive head-up tilt table test result with a heart rate-blood pressure product of less than 6000/min*mmHg.	All patients presenting with syncope and the following features; (1) no clinical or laboratory evidence of any cardiac, neurologic, or metabolic cause for the recurrent syncopal spells, and (2) positive response to head-up tilt testing. Age .35 years; ≥3 syncopal spells in the preceding 2 years, with the last episode occurring within 6 months of enrollment; and positive response to tilt table testing with syncope occurring in association with relative bradycardia. Relative bradycardia was defined as a trough heart rate, 60 bpm	≥3 syncopal episodes in previous 2 years, with the last episode occurring within 6 months of enrollment and with an interval between the first and the last episode of .6 months; Positive VASIS type 2A or 2B cardioinhibitory response to head-up tilt testing Age≥40 years or, if <40 years, proven refractoriness to conventional drug therapy.	≥6 syncopal episodes in previous 1 year Positive tilt-table test with syncope or presyncope and relative bradycardia.
Exclusion Criteria	NR	Cause of syncope was evident. They were also excluded if they had important valvular, coronary artery, or myocardial disease; an electrocardiographic abnormality; or any major non-CVD.	Cause of syncope other than vasovagal was known or even suspected. Patients were also excluded in case of any historic, clinical, or laboratory evidence of cardiac, neurologic, or metabolic disease. Other exclusion criteria included the need for any concomitant chronic pharmacologic treatment for any cause.	Cause of syncope other than vasovagal was known or suspected. Other exclusion criteria included recent (<6 months) myocardial infarction, severe heart failure (NYHA class III or IV), concomitant severe chronic diseases (e.g., diabetes mellitus, neurologic diseases, terminal diseases, and neoplasia), and patient refusal to participate in the study.	Cause other than vasovagal known or suspected. Valvular, coronary, myocardial, or conduction abnormality. Previous pacemaker therapy. Contraindication to pacemaker implantation. Major chronic non-CVD.
% with Syncope Screened Meeting Criteria	2.3%	NR	NR	3.5%	NR
N =	29	100	93	42	54
N Drivers =	NR	NR	NR	NR	NR
Mean Age ±SD: Years	PM group : 52 ±19 CT group : 54 ±18	PM group : 50.8±17.6 CT group : 47.8 ±17.7	58.2 years	PM group : 64 ±11 CT group : 56 ±14	PM group : 46 ±18 CT group : 40 ±18
% Male	PM group: 25.0 CT group: 46.2	PM group: 27.1 CT group: 51.9	40.9	PM group: 58 CT group: 57	PM group: 25 CT group: 30
Syncope Episodes (lifetime)	PM group: Median: 14 CT group: Median: 10	PM group: Median: 15 CT group: Median: 20	PM group: Median: 8 CT group: Median: 7	PM group: Median: 5 CT group: Median: 6	PM group: Median: 14 CT group: Median: 35

	Raviele et al.(203)	Connolly et al.(205)	Ammirati et al.(207)	Sutton et al.(208)	Connolly et al.(209)
Syncope Episodes (previous 6 months)	PM group: Median 4 CT group: Median: 2	PM group: Median: 4 (1 year) CT group: Median: 4 (1 year)	PM group: Median: 2 CT group: Median: 2	PM group: Median: 3 (2 years) CT group: Median: 3 (2 years)	PM group: Median: 3 (1 year) CT group: Median: 6 (1 year)
Number of Drugs Tried	PM group: Mean: 1.4 ±0.8 CT group: Mean: 1.5 ±1.1	PM group: 17 patients tried drugs CT group: 43 patients tried drugs	PM group: Mean: NR CT group: Mean: NR	PM group: NR CT group: NR	PM group: 17 patients tried drugs CT group: 15 patients tried drugs
% CMV Drivers	NR	NR	NR	NR	NR
Driving Exposure	NR	NR	NR	NR	NR
Generalizability to CMV Driver Population	Unknown	Unknown	Unknown	Unknown	Unknown

CMV Commercial motor vehicle.
CT Control.
NR Not reported.
NYHA New York heart association.
PM Pacemaker.
SD Standard deviation.

While the degree to which the findings of this study can be generalized to CMV drivers may be unclear, it is clear that the study enrollees are not representative of all individuals with recurrent syncope. This is evidenced by the fact that only 2.3% and 3.5% of individuals screened for inclusion in two of the included RCTs actually met study inclusion criteria.(203,208) Consequently, the findings of the studies discussed in this report are generalizable to a very small proportion of individuals with recurrent vasovagal syncope.

Findings

The five included studies and the outcome categories that they reported are listed in Table 55. Outcome data were available for all three of the outcomes of interest for the purposes of this report (proportion of patients experiencing recurrent syncope; time to recurrence of syncope; adverse events). All five articles addressed all three outcomes.

Table 55. Efficacy Outcomes Assessed

Reference	Year	Proportion of Patients Experiencing Recurrent Syncope	Time to Recurrence of Syncope	Adverse Events
Raviele et al.(203)	2004	✓	✓	✓
Connolly et al.(205)	2003	✓	✓	✓
Ammirati et al.(207)	2001	✓	✓	✓
Sutton et al.(208)	2000	✓	✓	✓
Connolly et al.(209)	1999	✓	✓	✓

Proportion of Patients Experiencing Syncope Recurrence during Follow-up

The proportion of individuals in each of the treatment arms of the five included studies who experienced at least one recurrence of vasovagal syncope during follow-up are presented in Table 56 and graphically in Figure 19. Three RCTs found that a significantly[23] smaller proportion of individuals treated with a dual-chamber implanted pacemaker experienced syncope recurrence when compared to controls. Two studies, both of which were double blinded, did not observe such a benefit.

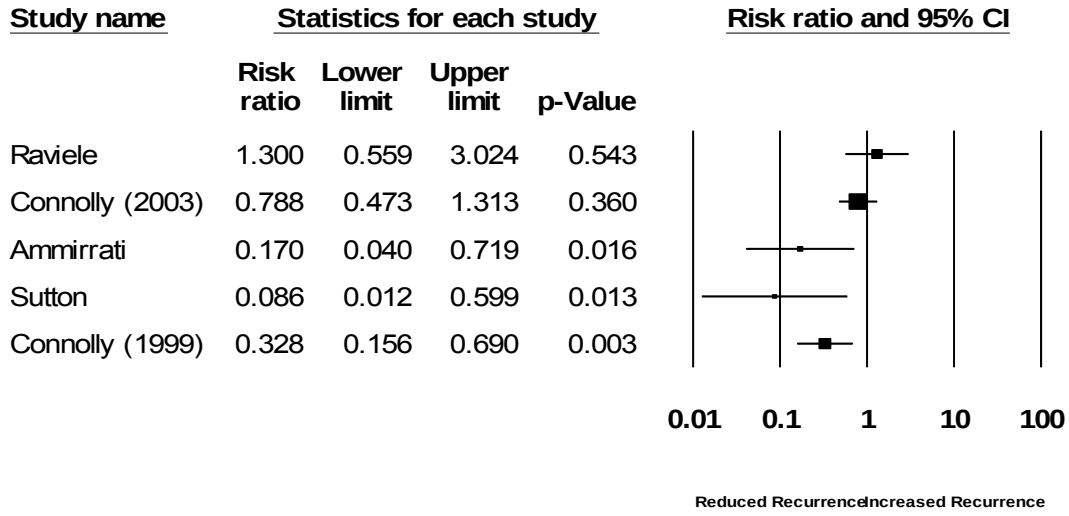
Table 56. Difference in Proportion of Patients Experiencing Syncope Recurrence during Follow-up

Reference	Year	Treatment Group	N =	Number of Patients with Recurrence	Follow-up Time	RR (95% CI)	*P* =	Pacemaker shown to be effective?
Raviele et al.(203)	2004	Pacemaker On	16	8	Pacemaker: Median: 563 days	1.30 (0.60–3.024)	0.543	No
		Pacemaker Off	13	5	Control: Median: 730 days			
Connolly et al.(205)	2003	Pacemaker On	48	16	Up to 6 months	0.79 (0.47–1.31)	0.360	No
		Pacemaker Off	52	22				
Ammirati et al.(207)	2001	Pacemaker	46	2	Mean: 35.4 months	0.17 (0.04–0.72)	0.016	Yes
		Pharmacologic Treatment	47	12				
Sutton et al.(208)	2000	Pacemaker	19	1	Mean: 3.7 years SD: 2.2 years Range: 1 to 6.7 years	0.09 (0.01–0.60)	0.013	Yes
		No Pacemaker	23	14				
Connolly et al.(209)	1999	Pacemaker	26	6	NR	0.33 0.16–0.69)	0.003	Yes
		No Pacemaker	27	19				

CI Confidence interval.
NR Not reported.
RR Rate ratio.
SD Standard deviation.

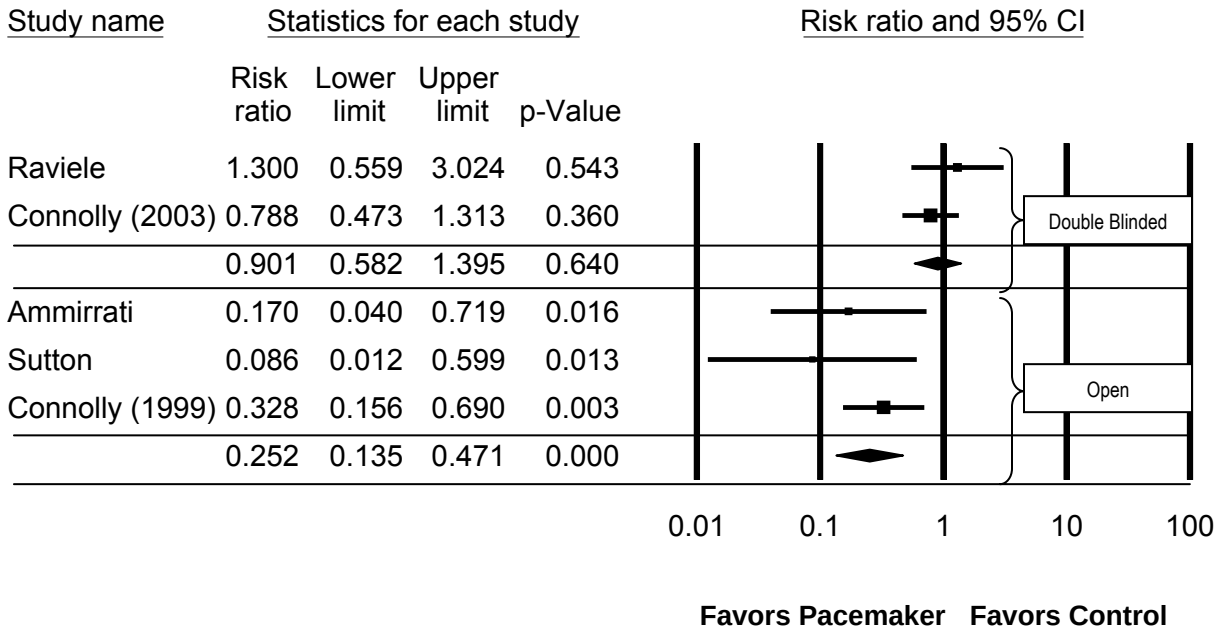
[23] Results achieved statistical significance.

Figure 19. Forest Plot of Syncopal Recurrence Rate Data



To determine whether the differences in the findings of the five studies were simply differences that one might expect to see as a consequence of pure chance, we subjected these data to homogeneity testing. The findings of this analysis found that the differences in the findings of the five studies are larger than would be expected than by chance alone ($Q = 13.63$, $P = 0.009$; $I^2 = 70.66$). A prespecified subgroup analysis (double blinded studies versus open studies) found that the two subgroups were significantly different from one another (Double-blind *RR* = 0.90, 95% CI: 0.58–1.34 versus Open RR = 0.25, 95% CI: 0.14–0.47; $Q = 10.70$, $P < 0.001$). The results of this analysis are shown graphically in Figure 20.

Figure 20. Findings of Prespecified Subgroup Analysis (Double Blinded versus Open Studies)

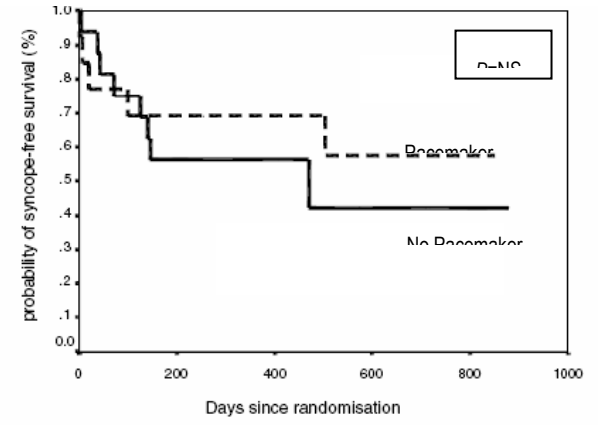


Time to First Recurrence of Syncope

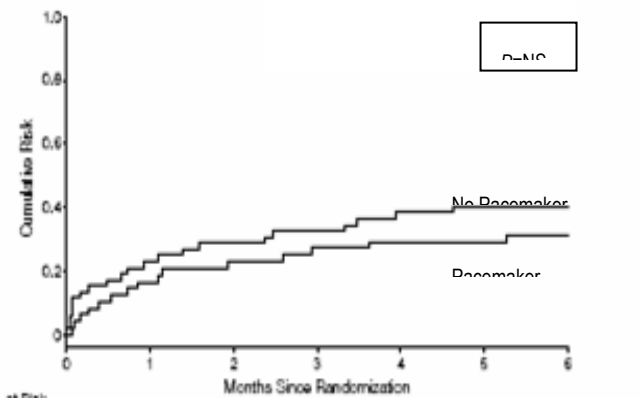
The most accurate method for determining whether there is a difference in the time to an event in two different groups within a study is to compare their Kaplan-Meier curves. All five included studies presented time to syncopal recurrence data in this manner (Figure 21).

Figure 21. Time-to-Syncopal Recurrence (Kaplan-Meier Curves)

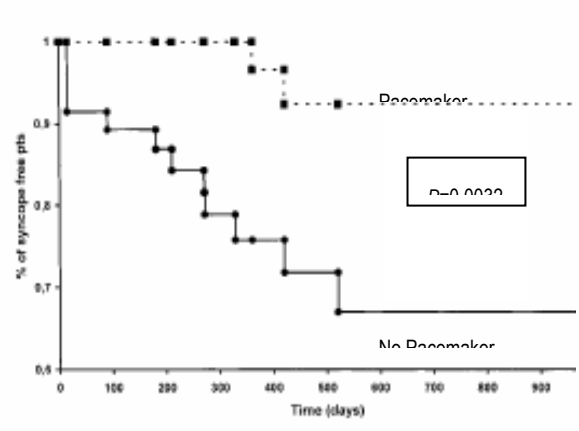
A. Raviele et al.



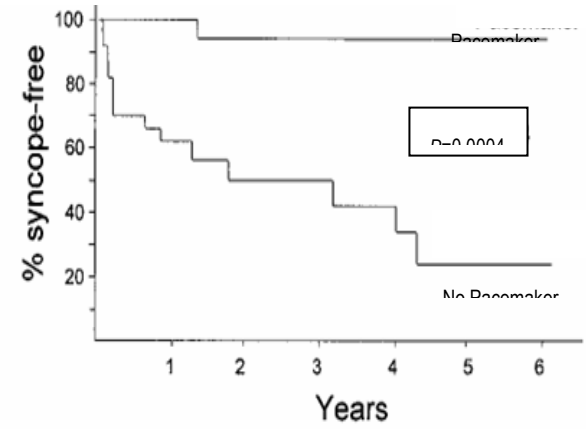
B. Connoly et al. 2003



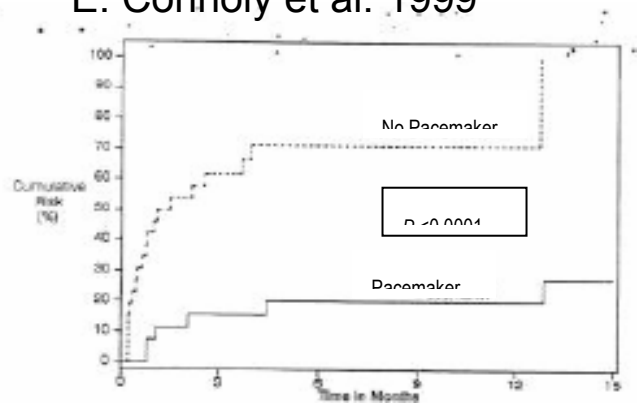
C. Ammirrati et al.



D. Sutton et al.



E. Connoly et al. 1999



In order to explore these data using meta-analytic techniques, the HR for each included study needed to be determined. Unfortunately, the information necessary to calculate the HR for each study (directly or indirectly) using the methods described by Parma et al.(3) was not presented in any of the five included studies. Thus, we are precluded from performing a meta-analysis of the time to syncopal event data in this evidence report and instead present the findings of a qualitative analysis of the data.[24]

Consistent with the findings of the previous analysis, the three early and unblinded RCTs all found that individuals with a pacemaker demonstrated large benefits over individuals in the control group. Such large benefits were not seen in the two more recent double-blinded RCTs.

Adverse Events Associated with Pacemakers

All five included studies reported on pacemaker-related adverse events that occurred during follow-up (Table 57). None of the adverse events that occurred as a consequence of pacemaker implantation or activity (i.e., infection, hematoma, pain) appeared to be incapacitating events that would be a cause for concern for those involved with motor vehicle driver safety.

Table 57. Adverse Events Associated with Pacemakers in Preventing Vasovagal Syncope Recurrence

Reference	Year	Active Pacemaker Arm	Control Arm
Raviele et al.(203)	2004	No deaths or severe syncope-related trauma. 6 cases: mild palpitations, possibly related to inappropriate device intervention. 2 cases: generator-related pain, one required repositioning of the device.	No deaths or severe syncope-related trauma. 1 case: Minor syncope-related injury.
Connolly et al.(205)	2003	No deaths or severe syncope-related trauma. 1 case: pericardial tamponade 4 cases: lead dislodgement 1 case: infection requiring antibiotics 1 case: wound hematoma 3 cases: pain related to pacemaker generator	No deaths or severe syncope-related trauma. 1 case: infection requiring reimplantation 3 cases: lead dislodgement 2 cases: infection requiring antibiotics 1 case: vein thrombosis 1 case: wound hematoma 1 case: pain related to pacemaker generator
Ammirrati et al.(207)	2001	No deaths or severe syncope-related trauma. 1 case minor syncope-related traumatic injuries. No local or systemic complications related directly to pacemaker implantation were reported. 5 cases: reported ≥1 episode of palpitations, possibly related to inappropriate pacemaker intervention.	No deaths or severe syncope-related trauma. 3 cases minor syncope-related traumatic injuries. 12 cases: reported mild-to-moderate side effects such as fatigue, depression, anxiety, and impotence. Symptoms considered to be directly related to the atenonol treatment. A titration decrement to 50 mg

[24] Graphical methods of estimating a HR from the Kaplan Meier curves presented in Figure 21 are available.(3) but these are extremely time consuming and require data on the number of individuals at risk at each time point. Such data was not presented by all five included studies. It was decided that the additional benefits that may be gained from utilizing these methods to meta-analyze a subgroup of the five included studies was not cost-effective.

Reference	Year	Active Pacemaker Arm	Control Arm
			required in 9 patients (19.5%). 1 patient required premature pharmacologic treatment discontinuation owing to intolerable side effects.
Sutton et al.(208)	2000	Two deaths occurred. None could be attributed to the pacemaker. One individual died of a stroke. The other died from cancer. 3 patients developed stable or paroxysmal second degree paroxysmal AV block.	No deaths
Connolly et al.(209)	1999	No deaths or severe syncope-related trauma. 1 case: lead dislodgement 5 cases: palpitations 1 case: pacemaker activity during rest	No deaths or severe syncope-related trauma.

AV Atrioventricular.

Section Summary

The best available evidence does not support the contention that permanent implanted dual-chamber pacemakers are effective in reducing the recurrence of vasovagal syncope in individuals with high recurrence rates (Strength of Evidence: Moderate).

- **Because of inconsistencies in the findings of the studies that comprise the evidence base for Key Question 3, we refrain from providing a single estimate of treatment effect at this time.**

  Five moderate-to-high quality RCTs addressed Key Question 3. Outcomes assessed by all five studies included the proportion of individuals experiencing recurrent syncope, the time to recurrence, and adverse events.

  Analysis of theses data found that the results of the high-quality (k = 2) and moderate-quality (k = 3) studies differed significantly. All three moderate-quality studies found that permanent dual-chamber pacemakers significantly reduce the number of recurrences of vasovagal syncope when compared to standard treatment. However, neither of the two high-quality studies found evidence to support the contention that permanent dual-chamber pacemakers offer an effective treatment option for individuals with recurrent syncope. The difference in findings may be attributed to a lack of blinding in the three moderate-quality studies in a group of individuals who are known to respond strongly to placebo.

Key Question 4: What is the risk of sudden incapacitation or sudden death following implantation of an ICD?

Background

ICDs

An ICD is a battery-powered, fully implantable device consisting of the device and one or more leads. These leads monitor heart rhythm and have the capacity to deliver an electrical shock to restore normal sinus rhythm when potentially life-threatening ventricular arrhythmias are detected. Cardioverter defibrillator implantation was initially a major operation requiring thoracotomy. At that time, defibrillation electrodes were patches sewn onto the myocardium with leads tunneled subcutaneously to the device that were implanted in a subcutaneous abdominal pocket. The implantation surgery was associated with 3% to 5% mortality. Modern implantable cardioverter defibrillators are transvenous systems, thus eliminating the need for thoracotomy and reducing mortality associated with implantation down to approximately 0.5%.

The ICD device is implanted either subcutaneously in the left or right deltopectoral area. In thin patients the ICD device is implanted subpectorally to prevent the device from eroding the skin. The ventricular lead tip is positioned in the right ventricular apex; a second lead can be positioned in the right atrial appendage to allow dual-chamber pacing if required and discrimination between atrial and ventricular tachycardias. The ventricular defibrillator lead has either one or two shocking coils. For two-coil leads, one is proximal (usually within the superior vena cava) and one is distal (right ventricular apex).

Early ICDs simply offered defibrillation shocks. Improvements in the technology mean that modern ICDs offer graded therapeutic responses to a sensed ventricular arrhythmia. Antitachycardia pacing, low-energy synchronized cardioversion, and high-energy defibrillation shocks can now be administered via a single transvenous lead. In addition, the devices can be programmed to detect and treat episodes of VT and VF. The devices precise, programmed values are being governed by the patient's clinical history, maximum sinus rate, and rates of any documented ventricular (and supraventricular) arrhythmias.

Separate 'zones' can be programmed for detection of VF (e.g., rate >200 to 220 per minute) and VT, with some devices allowing for two separate VT detection zones. Additional discriminatory features, such as sudden onset, beat-to-beat variability, QRS

width and/or morphology, and atrial rate can also be programmed to help discriminate between atrial and ventricular arrhythmias. Currently, ICDs are programmed for detection and treatment of both VF and VT in order to accommodate the development of new-onset VT (which frequently occurs after ICD implantation). VF is usually treated with shocks at the maximum energy of the device, but the ICD can be programmed to treat VT by a variety of modalities of antitachycardia pacing. If necessary, ICD can also be programmed to treat VT by low-energy cardioversion shocks.

Another important technologic advance in ICD development is the ability of the device to record intracardiac electrograms. This allows physicians to observe each episode of anti-tachycardia pacing or defibrillation to determine whether the ICD response was appropriate. It also allows physicians to make necessary changes to the ICD via a programming unit that is simply placed over the defibrillator site.

The Efficacy and Safety of ICDs

The overall efficacy and safety characteristics of ICDs have been evaluated in several large RCTs, systematic reviews, and meta-analyses. The findings of these primary and secondary studies provide strong evidence that ICDs reduce the risk for SCD among individuals at high risk for this adverse event (Table 58).

Complications associated with ICDs include infection; myocardium perforation, displacement, fracture, or insulation breakdown of the leads; oversensing or undersensing of the arrhythmia; and inappropriate shocks for sinus tachycardia or supraventricular tachycardia. Psychologic problems are common, and counseling plays an important role. RCTs that have evaluated patient quality of life (QOL) following implantation of an ICD are rare, and the little evidence that is available regarding QOL is inconsistent.(211,212) One finding common to studies that have reported on QOL is that the outcome closely correlates with the number of shocks delivered by the device. The greater the number of shocks delivered, the lower the individual's QOL. This finding supports data obtained from observational studies.(213,214)

Aside from issues pertaining to direct measures of safety and efficacy, another important issue related to ICDs' safety is their reliability. This issue was recently addressed by the U.S. Food and Drug Administration (FDA) in a publication of the findings of a review of data on pacemaker and ICD malfunctions submitted to them from 1990 to 2002.(215) Data collected included the number of pacemakers and ICD generators implanted during this time; the number of reported device malfunctions; and annual

malfunction replacement rates. Pacemakers and ICD generators were deemed to have malfunctioned when the device was explanted due to an observed malfunction, returned to the manufacturer, and confirmed by the manufacturer to be functioning inappropriately. Pacemaker and ICD replacement rates were defined as the annual number of replacements due to confirmed malfunction divided by the annual number of implants. Deaths were attributed to a device malfunction only if the death was witnessed. Leads and biventricular devices were not included in the study.

FDA reported that a total of 415,780 ICDs were implanted in the United States during the 12-year observation period. Of these, 8,489 ICDs (2%) were explanted due to a malfunction. The ICD malfunction replacement rate per 1,000 implants decreased from 38.6 in 1993 to 7.9 in 1996. However, this rate increased markedly during the latter half of the study, peaking in 2001 at 36.4 (P = 0.04 for trend) with more than half of the reported ICD malfunctions occurring in the last 3 years of the observation period. When compared to pacemakers, the overall ICD malfunction replacement rate was significantly higher (20.7 ±11.6 versus 4.6 ±2.2 replacements per 1,000 implants; RR = 5.9, 95% confidence interval, 2.7-9.1; P = 0.001). Thirty-one deaths were attributable to ICD malfunction.

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Table 58. Current Evidence on the Efficacy and Safety of ICDs

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Systematic Reviews and Meta-analyses							
Buxton et al.(216)	2006	Systematic Review	—	Patients enrolled in studies of primary and secondary SCD prevention studies.	Review concluded that there is increasing evidence for the effectiveness of ICD therapy compared with usual treatment in the management of ventricular arrhythmias, especially in patients with recurrent unstable arrhythmias and in prevention of additional life-threatening arrhythmias following survival of cardiac arrest, and in preventing SCD in those at high risk. The review authors note that indications for ICDs may be extended to include those with MI and heart failure. The review authors note that risk stratification tools and algorithms applicable to clinical settings are needed to identify those subgroups most likely to benefit from ICDs. In the light of conflicting conclusions on QOL from existing studies, the authors of the review note that further high-quality evidence on the QOL of patients with ICDs is required to show whether ICDs are superior to AADs. The reviewers note, however, that current evidence suggests that any overall differences in QOL must be relatively small. The reviewers also note that it is clear that the QOL for patients with ICDs is deleteriously affected by recurrent shocks.	NR	No
BCBS TEC(217)	2005	Systematic review and meta-analysis	—	Evaluates 10 trials that compared ICD to standard treatment. Primary and secondary prevention.	ICDs are effective in patients with acute MI and reduced LVEF and patients with no MI but reduced LVEF. Evidence on the efficacy of ICD use in patients with previous MI and reduced LVEF insufficient to draw an evidence-based conclusion.	Slightly increased risk for adverse events among individuals assigned to ICD group when compared to control groups.	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Ezekowitz et al.(218)	2003	Systematic review and meta-analysis	—	8 trials that compared ICD to standard care in patients at risk for SCD or ventricular arrhythmia.	Review concluded that ICDs reduce risk for SCD by 50% regardless of baseline risk, but impact on total mortality is sensitive to baseline risk for arrhythmic death. The evidence reported showed support for the use of ICDs in secondary prevention or for primary prevention in high-risk groups (e.g., patients with coronary artery disease and severe left ventricular dysfunction). The evidence did not show a significant impact on total mortality rates in patients at lower risk for SCD (e.g., patients with left ventricular dysfunction but no coronary artery disease or inducible ventricular arrhythmias).	Complication rates were higher for transthoracic ICDs. The more recent trials, which used newer ICD models, reported lower complication rates.	No
Lee et al.(219)	2003	Systematic review and meta-analysis	—	9 primary and secondary SCD prevention trials that compared ICD to standard care.	Review concluded that ICDs decrease the risk for arrhythmic death. Its influence on all-cause mortality, however, is related to the underlying risk of arrhythmia-related death relative to competing causes. The reviewers noted that given the cost of the device strategy, policies of targeted intervention based on future risk for arrhythmia are warranted.	Perioperative death occurred in 1.2% Infection occurred in 2.4% Hematoma or seroma occurred in 3.7% Pericardial effusion or tamponade occurred in 0.6% Pneumothorax occurred in 1.6% Lead dislodgement or fracture occurred in 2.3% Device malfunction occurred in 2.0%	No
Connolly et al.(220)	2000	Meta-analysis of data from AVID, CASH, and CIDS	—	Patients enrolled on AVID, CASH, and CIDS (studies of secondary prevention).	Meta-analysis showed a significant reduction in death from any cause with the ICD; with a summary hazard ratio (ICD: amiodarone) of 0·72 (95% confidence interval 0·60, 0·87; *P* = 0·0006). For the outcome of arrhythmic death, the hazard ratio was 0·50 (95% confidence interval 0·37, 0·67; *P* <0·0001). Survival was extended by a mean of 4·4 months by the ICD over a follow-up period of 6 years. Patients with LVEF ≤35% derived significantly more benefit from ICD therapy than those with better preserved left ventricular function. Patients treated before the availability of nonthoracotomy ICD implants derived significantly less benefit from ICD therapy than those treated in the nonthoracotomy era.	NR	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Parkes et al.(221)	2001	Systematic review	–	Patients enrolled in 7 RCTs designed to assess effectiveness of primary and secondary SCD prevention studies.	Studies demonstrated changes in absolute risk of total mortality ranging from an increase of 1.7% to a reduction of 22.8% (RRR range: –7% to +54%). The estimated benefits of ICDs from RCT data in terms of increased years of life were 0.23–0.8 additional years of life when compared with antiarrhythmic drug therapy.	**Peri-insertion complications** o *Mortality:* This is now reported to be less than 1% with transvenous compared with transthoracic insertion of devices. o *Inability to insert device:* The smaller device size and transvenous approach have increased the number of patients in whom insertion of ICD is possible. o *Lead dislodgement:* This is the most common of the perioperative complications (range of 1% to 10%). Appears to be related to experience of surgeon implanting ICD. o *Infection:* Appears to be around 4% or less with the transvenous approach. Becomes apparent within 60 days of implantation. o *Hematomas and bleeding:* A wide range of wound-related problems after insertion have been reported. Use of concurrent anticoagulation, the muscular pocket used to implant the device and use of subcutaneous leads may be associated with this disbenefit. o *Perforation of heart and lungs:* This was reported as very uncommon. **Device failure** o *Proarrhythmia:* A recognized complication of ICD. Many iatrogenic arrhythmias are terminated by the ICD. This can have deleterious effects on patients, who experience a series of uncomfortable additional shocks after the ICD has induced arrhythmia. There are at least three reported fatalities in the literature. o *Failure to detect an arrhythmia/inappropriate Intervention*: ICDs cannot easily differentiate between VTs and SVTs and may be activated inappropriately by the latter. Inappropriate shocks may cause an arrhythmia, cause the patient discomfort and psychologic harm, and reduce the battery life of the device. This complication has been reduced by the use of dual-chamber sensing devices in the most recent ICDs, but this increases the initial cost of the device.	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Cost-effectiveness analyses							
Sanders et al.(222)	2005	CEA	NA	Study assessed the cost-effectiveness of the ICD in the populations represented in eight primary-prevention trials. Primary prevention trials evaluated whether the prophylactic use of an implantable cardioverter defibrillator (ICD) improves survival among patients who are at risk for sudden death due to left ventricular systolic dysfunction but who have not had a life-threatening ventricular arrhythmia.	Authors found that ICD increased lifetime costs in every trial. Two trials — the Coronary Artery Bypass Graft (CABG) Patch Trial and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) — found that the prophylactic implantation of an ICD did not reduce the risk of death and thus was both more expensive and less effective than control therapy. For the other six trials — the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I, MADIT II, the Multicenter Unsustained Tachycardia Trial (MUSTT), the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) — the use of an ICD was projected to add between 1.01 and 2.99 quality-adjusted life years (QALY) and between $68,300 and $101,500 in cost. Using base-case assumptions, investigators found that the cost-effectiveness of the ICD as compared with control therapy in these six populations ranged from $34,000 to $70,200 per QALY gained. Sensitivity analyses showed that this cost-effectiveness ratio would remain below $100,000 per QALY as long as the ICD reduced mortality for seven or more years.	NR	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Al-Khatib et al.(223)	2005	CEA	NA	Patients met MADIT-II eligibility criteria and were enrolled in the Duke Cardiovascular Database between January 1, 1986 and December 31, 2001.	Investigators found that compared with conventional medical therapy, ICDs projected to result in an increase of 1.80 discounted years in life expectancy and an incremental cost-effectiveness ratio of $50,500 per life-year gained. Cost-effectiveness varied dramatically with changes in time horizon: The cost-effectiveness ratio increased to $67,800 per life-year gained, $79,900 per life-year gained, $100,000 per life-year gained, $167,900 per life-year gained, and $367,200 per life-year gained for 15-year, 12-year, 9-year, 6-year, and 3-year time horizons, respectively. Changing the frequency of follow-up visits, complication rates, and battery replacements had less of an effect on the cost-effectiveness ratios than reducing the cost of ICD placement and leads.	NR	No
Hlatky et al.(224)	2004	CEA	NA	No details given. Data from three RCTs (MADIT, AVID, CIDS)	ICD therapy is cost-effective when it prolongs life by ≥6 months. This occurs in individuals who are at highest risk for sudden-cardiac death.	NR	No
Owens et al.(225)	2002	CEA	NA	No details given. Inputs based on data from randomized clinical trials, registries, and meta-analyses.	The relationship between cost-effectiveness of the ICD and the total annual cardiac mortality rate is U-shaped; cost-effectiveness becomes unfavorable at both low and high total cardiac mortality rates. If the annual total cardiac mortality rate is 12%, the cost-effectiveness of the ICD varies from $36,000 per QALY gained when the ratio of sudden cardiac death to non-sudden cardiac death is 4 to $116,000 per QALY gained when the ratio is 0.25.	NR	No
Spath et al.(226)	2002	CEA	NA	Patients enrolled in nine trials in which ICD compared to drug therapy. All patients at high risk for VF/VT.	Authors commented that cost effectiveness was in the order of $20 to $60,000 per life-year gained. Stratification of the data showed that individuals with the highest risk for VF/VT (LVEF ≤35%) gained most from implant.	NR	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
RCTs							
Bardy et al.(227)	2005	RCT	SCD-HeFT	New York Heart Association (NYHA) class II or III CHF and a LVEF of 35% or less.	The median LVEF in patients was 25%; 70% were in NYHA class II, and 30% were in class III CHF. The cause of CHF was ischemic in 52% and nonischemic in 48% The median follow-up was 45.5 months. There were 244 deaths (29%) in the placebo group, 240 (28%) in the amiodarone group, and 182 (22%) in the ICD group. As compared with placebo, amiodarone was associated with a similar risk of death (hazard ratio, 1.06; 97.5% confidence interval, 0.86 to 1.30; P = 0.53), and ICD therapy was associated with a decreased risk of death of 23% (0.77; 97.5% confidence interval, 0.62 to 0.96; P = 0.007) and an absolute decrease in mortality of 7.2% points after 5 years in the overall population. Results did not vary according to either ischemic or nonischemic causes of CHF, but they did vary according to the NYHA class.	Clinically significant ICD complications, defined as clinical events requiring surgical correction, hospitalization, or new and otherwise not anticipated drug therapy, occurred in 5% of the patients at the time of implantation and in 9% later in the course of the trial. No further details given.	No
Hohnloser et al.(228)	2004	RCT	DINAMIT	Patients who had recently experienced an acute MI with reduced LVEF (≤35%) and impaired cardiac autonomic function.	During a mean (±SD) follow-up period of 30 ±13 months, there was no difference in overall mortality between the two treatment groups: of the 120 patients who died, 62 were in the ICD group and 58 in the control group (hazard ratio for death in the ICD group, 1.08; 95% confidence interval, 0.76 to 1.55; P = 0.66). There were 12 deaths due to arrhythmia in the ICD group, as compared with 29 in the control group (hazard ratio in the ICD group, 0.42; 95% confidence interval, 0.22 to 0.83; P = 0.009). In contrast, there were 50 deaths from nonarrhythmic causes in the ICD group and 29 in the control group (hazard ratio in the ICD group, 1.75; 95% confidence interval, 1.11 to 2.76; P = 0.02).	The average time between randomization and ICD implantation was 6.3±7.3 days. Of the 332 patients assigned to receive an ICD, 310 actually received a device. The time between ICD implantation and discharge from the hospital averaged 4.7±6.4 days. In hospital device-related complications occurred in 25 patients; the most common of these complications were lead dislodgment, pneumothorax, and inappropriate shocks. There were no deaths related to device implantation. To prevent inappropriate pacing, bradycardia pacing was typically programmed to 40 to 45 beats per minute (maximum, 55 beats per minute).	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Kadish et al.(229)	2004	RCT	DEFINITE	Patients with nonischemic dilated cardiomyopathy, a LVEF ≤35%, and premature ventricular complexes or nonsustained VT.	Patients followed for a mean (±SD) of 29.0 ±14.4 months. Mean LVEF = 21%. Majority of patients were treated with angiotensin-converting–enzyme (ACE) inhibitors (86%) and beta blockers (85%). There were 68 deaths: 28 in the ICD group, as compared with 40 in the standard-therapy group (hazard ratio, 0.65; 95% confidence interval, 0.40 to 1.06; P = 0.08). The mortality rate at 2 years was 14.1% in the standard-therapy group (annual mortality rate, 7%) and 7.9% in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard therapy group (hazard ratio, 0.20; 95% confidence interval, 0.06 to 0.71; P = 0.006).	NR	No
Connolly et al.(230,231)	2000	RCT	CIDS	Patients who, in the absence of either recent acute MI (≤72 hours) or electrolyte imbalance, manifested any of the following: (1) documented VF; (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion; (3) documented, sustained VT causing syncope; (4) other documented, sustained VT at a rate ≥150 beats/minute, causing presyncope or angina in a patient with a LVEF ≤35%; or (5) unmonitored syncope with subsequent documentation of either spontaneous VT or sustained (≥30 seconds) monomorphic VT induced by programmed ventricular.	RRR at 5 years: 19.7% with ICD (*P* = 0.142)	Complications at 3 years follow-up included: • 5.1% infection rate • 2.6% lead fracture	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Moss et al.(232)	2002	RCT	MADIT II	Patients with previous MI and heart failure with LVEF <30%.	ICD conferred a survival advantage (RRR 30%, ARR 6%) over usual treatment. This benefit was greater in those with a higher risk of mortality. Benefit appeared after 9 months following implantation, which contrasts with results from MADIT I, where survival rate improved in the first few months. This may be due to lower mortality in the conventional therapy arm in MADIT II, the lower LVEF cut-off used, the absence of risk stratification of arrhythmias as entry criteria, and the more intensive use of medical treatment. Subgroup analysis showed a similar benefit of ICDs regardless of age, gender, NYHA heart failure class, and QRS duration.	Adverse events occurring in patients with ICD included: • 13 lead dislodgements • 5 infections • 148 worsening heart failure It is unclear whether the increased hospitalization rate of ICD patients with worsening heart failure was due to patients living longer and having time for their heart failure to deteriorate, or it may be associated with the devices.	No
Bansch et al.(233)	2002	RCT	CAT	Patients with dilated cardiomyopathy of recent onset with impaired left ventricular function.	An interim analysis was conducted after recruitment of 100 patients with at least 1 year of follow-up in 1997. This showed that overall mortality for all patients was 5.6%, with a difference in survival between the two groups of 2.6%. Further follow-up and survival analysis in 2000 showed no difference between the groups. The only predictor of total mortality was impaired LVEF. The authors conclude that ICDs did not confer any survival benefit in these patients, including those with lower LVEF and nonsustained VTs. The study was underpowered to detect differences because of the low event rate, which is likely to have led to the lack of survival benefits from ICDs.	Adverse events occurring in patients with ICD included: • 2 revisions due to bleeding and dislocation • 9 electrode dislodgements • 2 infections • 1 cardiac perforation	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Kuck et al.(234,235)	2000	RCT	CASH	Patients were survivors of cardiac arrest.	ICD reduced relative risk of absolute mortality observed when compared to pharmacotherapy with amiodarone or metoprolol at 2 years. Follow-up (risk reduction = 37% P = 0.081)	Adverse events occurred in 23% of patients with ICD • 5 died perioperatively • 3 epicardial device infections • 2 explantations • 6 hematomas • 1 pericardial effusion • 3 plural effusions • 1 pneumothorax • 3 dislodgements/lead migrations • 2 device malfunctions	No
Buxton et al.(236-238)	1999	RCT	MUSTT	Patients with CHD, non-sustained VT. LVEF <40%, and EP-diagnosed inducible sustained VT.	ICD reduced the risk for all-cause mortality by 13% when compared to conservative management over a mean FUT of 39 months.	0.7% of individuals with ICD experienced inducible, sustained, nonfatal VT.	No
AVID Investigators(239)	1997	RCT	AVID	Patients who experienced cardiac arrest survivors (45%) or sustained VT with syncope, or symptomatic sustained VT (55%) with LVEF <40%.	ICD reduced total mortality by 37% at 1 year follow-up, 22% at 2 year follow-up, 23% at 3 years follow-up when compared to pharmacotherapy with amiodarone or sotalol (*P* <0.02).	Adverse events occurred in 19/507 patients with ICD: • 6 bleedings • 13 hematomas • 10 infections • 8 pneumothoraxes • 1 cardiac perforation	No

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety		Impact on driving considered?
Bigger et al.(240)	1997	RCT	CABG-Patch	Patients with coronary heart disease, left ventricular dysfunction, and abnormalities on signal-averaged electrocardiograms have an increased risk of sudden death.	During an average (SD) follow-up of 32 (16) months, there were 101 deaths in the defibrillator group (71 from cardiac causes) and 95 in the control group (72 from cardiac causes). The hazard ratio for death from any cause was 1.07 (95% confidence interval, 0.81 to 1.42; *P* = 0.64). There was no statistically significant interaction between defibrillator therapy and any of 10 preselected base-line covariates.	Complication	%	No
						Postoperative complications		
						Myocardial infarction	4.0	
						Sustained ventricular tachycardia	5.8	
						Ventricular fibrillation	3.4	
						Bradycardia	2.9	
						Atrial fibrillation	22.9	
						Shock	9.2	
						New or more severe heart failure	15.7	
						Conduction defect	14.1	
						Residual central nervous system deficit	3.6	
						Bleeding treated with surgery	4.9	
						Postpericardiotomy syndrome	0.9	
						Deep sternal-wound infection	2.7	
						Infection at wound or catheter site	12.3	
						Pneumonia	8.5	
						Other infection	6.3	
						Renal failure	6.7	
						Events during long-term follow-up		
						Angina pectoris	27.0	
						Myocardial infarction	0.5	
						New or worsening heart failure	42.5	
						Ventricular arrhythmias	19.4	
						Atrial fibrillation	14.7	
						Hospitalization	61.4	
						PTCA or atherectomy	2.9	
						Permanent cardiac pacemaker	2.9	

Reference	Year	Study Type	Study Name (if applicable)	Patient Population	Efficacy	Safety	Impact on driving considered?
Moss et al.(241)	1996	RCT	MADIT	Patients experienced MI ≥3 weeks before entry, with documented asymptomatic unsustained VT unrelated to MI, LVEF ≤0.35, with inducible VT not suppressed by procainamide, NYHA functional class I, II or III, no indications for CABG or angioplasty within 3 months.	ICD reduced the risk of SCD by 54% when compared to conventional therapy over a mean FUT of 27 months (RR = 0.46; 95% CI: 0.26–0.82); *P* = 0.009)	Adverse events occurred in 19/95 individuals with ICD: • 2 pneumothoraxes • 2 infections • 7 lead problems • 7 rhythm problems	No
Wever et al.(242)	1995	RCT	—		RR of death in ICD arm: 0.27 (95% CI 0.09 to 0.85; *p* = 0.02)	Adverse events occurred in 2 patients with ICD: • 1 lead migration • 1 infection	No

AADs	Antiarrthymia drugs.
ACE	Angiotensin-converting-enzyme.
ARR	Absolute risk reduction.
AVID	Antiarrhythmics versus implantable defibrillators.
CABG	Coronary artery bypass grafting.
CASH	Cardiac arrest study Hamburg.
CAT	Cardiomyopathy trial.
CEA	Cost-effectiveness analysis.
CHF	Congestive heart failure.
CI	Confidence interval.
CIDS	Canadian implantable defibrillator study.
COMPANION	Comparison of medical therapy, pacing, and defibrillation in heart failure.
DEFINITE	Defibrillators in nonischemic cardiomyopathy treatment evaluation.
DINAMIT	Defibrillator in acute myocardial infarction trial.
FUT	Follow-up time.
ICD	Implantable cardioverter defibrillator.
LVEF	Left ventricular ejection fraction.
MADIT	Multicenter automatic defibrillator implantation trial.
MI	Myocardial infarction.
MUSTT	Multicenter unsustained tachycardia trial.
NA	Not applicable.
NR	Not reported.
NYHA	New York Heart Association.
PTCA	Percutaneous transluminal coronary angioplasty.
QALY	Quality-adjusted life years.
QOL	Quality of life.
RCTs	Randomized controlled trials.

RR	Rate ratio.
RRR	Rate risk reduction.
SCD	Sudden cardiac death.
SD	Standard deviation.
SVT	Supraventricular tachycardia.
VT	Ventricular tachycardia.

Clinical Practice Guidelines and Standards

Several organizations have released clinical practice guidelines and standards pertaining to the use of ICDs in patients with CVD. We have summarized these clinical practice guidelines and standards below into two subgroups: those that address the issue of ICDs and driving and those that provide guidance on the appropriate use of the devices. The former subgroup provides information on the position of various professional bodies pertaining to the appropriateness of driving with an ICD. The latter subgroup provides information of the position of professional bodies on the appropriate use of ICDs. Although guidelines and standards that fall into this latter category do not provide information pertinent to driving, they do provide important insight into the characteristics of individuals considered to be appropriate candidates for an ICD.

Guidelines and Standards Pertaining to ICDs and Driving

CCS Consensus Conference 2004: Assessment of the Cardiac Patient for Fitness to Drive(243)

The recommendations of the Canadian Cardiovascular Society (CCS) as they pertain to driving following the implantation of an ICD are summarized in Table 59.

Table 59. Recommendation of CCS Regarding Driving and ICDs

Reason for Implantation	Recommendation	
	Private Driving	Commercial Driving
Primary prophylaxis; NYHA class I to III	4 weeks after implant	Disqualify†
A primary prophylaxis ICD has been recommended but declined by the patient	No restriction	Disqualify†
Secondary prophylaxis for VF or VT with decreased level of consciousness; NYHA class I to III	6 months after event*	Disqualify†
Secondary prophylaxis for sustained VT with no accompanying decreased level of consciousness; NYHA class I to III	1 week post-implant, in addition to the appropriate waiting period for the ventricular tachyarrhythmia	Disqualify†
Any event resulting in device therapies being delivered (shock or ATP), in which level of consciousness was impaired, or the therapy(ies) delivered by the device was/were disabling	Additional 6-month restriction	Disqualify†

* The 6-month period begins not at the time of ICD implant, but rather at the time of the last documented episode of sustained symptomatic ventricular tachycardia (VT) or syncope judged to be likely due to VT or cardiac arrest. For patients who have a bradycardia indication for pacing as well, the additional criteria under section II (6) also apply. All patients must be followed from a technical standpoint in a device clinic with appropriate expertise

† ICDs may sometimes be implanted in low-risk patients. Individual cases may be made for allowing a commercial driver to continue driving with an ICD provided the annual risk of sudden incapacitation is believed to be 1% or less.

ATP Antitachycardia pacing.
ICD Implantable cardioverter defibrillator.
NYHA New York Heart Association.
VF Ventricular fibrillation.
VT Ventricular tachycardia.

DoT/FMCSA Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Driver: 2002(1)

FMCSA's 2002 Cardiovascular Advisory Panel (CAP) noted that ICDs do not prevent arrhythmias and that the risk for sudden incapacitation due to a loss of consciousness or sudden death in patients implanted with these devices, though reduced, is not eliminated. Consequently, the CAP recommended that all individuals with an ICD be disqualified from driving a CMV.

The Driving and CVD Task Force of the European Society of Cardiology(244)

In 1998, the Driving and CVD Task Force of the European Society of Cardiology (ESC) published a series of guidelines for those physicians who were required to advise individuals with CVD about their fitness to drive. The ESC Task Force recommended that Grade 2 drivers (European drivers of trucks and buses comparable to CMV drivers in the United States) who receive an ICD should be permanently excluded from driving. ESC noted that its concerns regarding the relationship of ICD devices to road traffic crashes were based on three theoretical considerations: 1) the devices were implanted into patients at high risk of collapse, often those with coronary heart disease, previous cardiac arrest, and poor left ventricular function; 2) device discharge or treatment was accompanied by involuntary movement and potential incapacitation; and 3) the reliability of the device was uncertain and false triggering, either from device and lead malfunction or from a relatively benign arrhythmia, was considered a probable occurrence. ESC also noted that its position on driving and ICDs might require alteration with the advent of new evidence. At the time of writing the present evidence report no updates to these current guidelines have been published.

Guidelines and Standards Pertaining to the Appropriate Use of ICDs in Individuals with CVD

Below we provide information from published clinical practice guidelines that pertain to the indications for ICDs. All guidelines represented in this section are evidence-based (i.e., the guideline developers used systematic approaches to evaluate relevant evidence).

ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death(245)

The American College of Cardiology (ACC), the American Heart Association (AHA), and ECS provide the following guidance pertaining to the use of ICDs in patients with ventricular arrhythmias:

1. If coronary revascularization cannot be carried out and there is evidence of prior MI and significant left ventricular (LV) dysfunction, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: A*[25]*)*
2. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an left ventricular ejection fraction (LVEF) less than or equal to 30% to 40%, are New York Heart Association (NYHA) functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
3. ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with hemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
4. ICD implantation is reasonable in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30% to

[25] Level A Evidence = recommendation derived using data from several randomized controlled trials or a meta-analysis;
Level B Evidence = recommendation derived using data from a single randomized controlled trial or several non-randomized studies;
Level C Evidence = recommendation derived from consensus opinion, case studies, or standard of care.

35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: B)*

5. Adjunctive therapies to the ICD, including catheter ablation or surgical resection and pharmacologic therapy with agents such as amiodarone or sotalol, are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI. *(Level of Evidence: C)*
6. If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
7. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
8. The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with hemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
9. ICD implantation is reasonable in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
10. Adjunctive therapies to the ICD, including catheter ablation or surgical resection and pharmacologic therapy with agents such as amiodarone or sotalol, are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI. *(Level of Evidence: C)*
11. ICD implantation is indicated in patients with congenital heart disease who are survivors of cardiac arrest after evaluation to define the cause of the event and exclude any reversible causes. ICD implantation is indicated in

patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. Patients with congenital heart disease and spontaneous sustained VT should undergo invasive hemodynamic and E-prostanoid (EP) evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended. *(Level of Evidence: C)*

12. Invasive hemodynamic and EP evaluation is reasonable in patients with congenital heart disease and unexplained syncope and impaired VF. In the absence of a defined and reversible cause, ICD implantation is reasonable in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: B)*
13. ICD implantation can be beneficial in patients with life-threatening ventricular arrhythmias who are not in the acute phase of myocarditis, as indicated in the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (see below), who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: C)*
14. ICD implantation is not indicated during the acute phase of myocarditis. *(Level of Evidence: C)*
15. In addition to managing the underlying infiltrative cardiomyopathy, life-threatening arrhythmias should be treated in the same manner that such arrhythmias are treated in patients with other cardiomyopathies. This includes the use of ICD and pacemakers in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: C)*
16. Persistent life-threatening ventricular arrhythmias that develop in patients with endocrine disorders should be treated in the same manner that such arrhythmias are treated in patients with other diseases. This includes use of ICD and pacemaker implantation as required in those who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: C)*
17. Life-threatening ventricular arrhythmias, especially in patients awaiting renal transplantation, should be treated conventionally. This includes the use of ICD and pacemaker implantation as required in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of

survival with a good functional status for more than one year. *(Level of Evidence: C)*

18. Life-threatening ventricular arrhythmias in patients with obesity, anorexia, or a dieting plan should be treated in the same manner that such arrhythmias are treated in patients with other diseases. This includes ICD and pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: C)*
19. Ventricular arrhythmias that develop in patients with pericardial disease should be treated in the same manner that such arrhythmias are treated in patients with other diseases. This includes ICD and pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: C)*
20. An ICD should be implanted in patients with nonischemic dialated cardiomyopathy (DCM) and significant LV dysfunction who have sustained VT or VF, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: A)*
21. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic DCM who have an LVEF less than or equal to 30% to 35%, who are NYHA functional class II or III, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
22. ICD implantation can be beneficial for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. ICD implantation can be effective for termination of sustained VT in patients with normal or near normal ventricular function and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
23. Placement of an ICD might be considered in patients who have nonischemic DCM, LVEF of less than or equal to 30% to 35%, who are NYHA functional class I receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

24. ICD therapy should be used for treatment in patients with hypertrophic cardiomyopathy (HCM) who have sustained VT and/or VF and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. *(Level of Evidence: B)*
25. ICD implantation can be effective for primary prophylaxis against SCD in patients with HCM who have one or more major risk factors (see Table 60) for SCD and who are receiving chronic optimal medical therapy. ICD implantation can also be effective in patients who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*

Table 60. Risk Factors for SCD in HCM

Major Risk Factors	Possible in Individual Patients
Cardiac arrest (VF)	AF
Spontaneous sustained VT	Myocardial ischemia
Family history of premature sudden death	LV outflow obstruction
Unexplained syncope	High-risk mutation
LV thickness greater than or equal to 30 mm	Intense (competitive)
Abnormal exercise BP	Physical exertion
Nonsustained spontaneous VT	

From: ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death.(245)

AF Atrial fibrillation.
BP Blood pressure.
LV Left ventricular.
VF Ventricular fibrillation.
VT Ventricular tachycardia.

26. ICD implantation is recommended for the prevention of SCD in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) with documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
27. ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease. This includes those with LV involvement, one or more affected family members with SCD or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, those who are receiving chronic optimal medical therapy, and those who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
28. ICD therapy is recommended for secondary prevention of SCD in patients who survived VF, hemodynamically unstable VT, or VT with syncope. It is also

recommended for those who have an LVEF less than or equal to 40%, who are receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*

29. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
30. ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
31. Amiodarone, sotalol, and/or other beta blockers are recommended pharmacologic adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure (HF). *(Level of Evidence: C)*
32. ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD in patients with NYHA functional class III or IV, who are receiving optimal medical therapy, who are in sinus rhythm with a QRS complex of at least 120 ms, and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
33. ICD therapy is reasonable for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)* (See Section 1.2.)
34. ICD therapy is reasonable in patients who have recurrent stable VT, a normal or near normal LVEF, and optimally treated HF. Patients must also have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
35. ICD therapy may be considered for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease

who have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*

36. ICD implantation along with use of beta blockers is recommended for Long QT Syndrome (LQTS) patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: A)*
37. ICD implantation with continued use of beta blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
38. An ICD is indicated for Brugada syndrome patients with previous cardiac arrest who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
39. An ICD is reasonable for Brugada syndrome patients with spontaneous ST-segment elevation in V1, V2, or V3 who have had syncope with or without mutations demonstrated in the *SCN5A* gene. ICD is also acceptable for those who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
40. ICD implantation with use of beta blockers is indicated for patients with cathecholaminergic polymorphic ventricular tachycardia (CPVT) who are survivors of cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
41. ICD implantation with the use of beta blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta blockers. ICD implantation can also be effective for those who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
42. ICD implantation can be effective therapy for the termination of sustained VT in patients with normal or near-normal ventricular function and no structural heart disease who are receiving chronic optimal medical therapy and who have reasonable expectation of survival for more than 1 year. *(Level of Evidence: C)*
43. Persistent life-threatening ventricular arrhythmias, despite abstinence from alcohol, should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including an ICD, as required. Patients

receiving chronic optimal medical therapy and those who have reasonable expectation of survival for more than 1 year should also be treated in that manner. *(Level of Evidence: C)*

44. Elderly patients with projected life expectancy less than 1 year due to major comorbidities should not receive ICD therapy. *(Level of Evidence: C)*
45. An ICD should be implanted in pediatric survivors of a cardiac arrest when a thorough search for a correctable cause is negative, when patients are receiving optimal medical therapy, and when they have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
46. ICD therapy in conjunction with pharmacologic therapy is indicated for high-risk pediatric patients with a genetic basis (ion channel defects or cardiomyopathy) for either SCD or sustained ventricular arrhythmias. The decision to implant an ICD in a child must include consideration the risk of SCD associated with the disease, and the potential equivalent benefit of medical therapy. Other factors that must be considered are the risks of device malfunction, infection, or lead failure. In addition, children must have a reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: C)*
47. ICD therapy is reasonable for pediatric patients with spontaneous sustained ventricular arrhythmias associated with impaired (LVEF of 35% or less) ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
48. ICD therapy is reasonable for pediatric patients with spontaneous sustained ventricular arrhythmias associated with impaired (LVEF of 35% or less) ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year. *(Level of Evidence: B)*
49. Patients with implanted ICDs should receive regular follow-up and analysis of the device status. *(Level of Evidence: C)*
50. Implanted ICDs should be programmed to obtain optimal sensitivity and specificity. *(Level of Evidence: C)*
51. Measures should be undertaken to minimize the risk of inappropriate ICD therapies. *(Level of Evidence: C)*
52. Patients with implanted ICDs who present with incessant VT should be hospitalized for management. *(Level of Evidence: C)*

The UK National Institute of Clinical Excellence (NICE): 2006 Update

NICE published its original guidelines on the use of ICDs in individuals with CVD in 2000.(246) These guidelines were updated in 2006 with the publication of a NICE "Review of Technology Appraisal."(247) The updated guidelines expanded NICE's original recommendations on the appropriate use of ICDs for the primary prevention of SCD to include patients with an LVEF of less than 30% (no worse than class III of NYHA functional classification of heart failure) and a QRS duration of equal to or more than 120 ms, without the need for electrophysiologic testing. It also includes patients who have undergone surgical repair for congenital heart conditions.

The 2006 guidelines recommended by NICE state that the use of ICDs should be routinely considered for the following circumstances:

1. "Secondary prevention," that is, for patients who present, in the absence of a treatable cause, with one of the following:
    - Having survived a cardiac arrest due to either VT or VF.
    - Spontaneous sustained VT causing syncope or significant hemodynamic compromise.
    - Sustained VT without syncope or cardiac arrest, and who have an associated reduction in EF (LVEF of less than 35%) (no worse than class III of the NYHA functional classification of HF).
2. "Primary prevention," that is, for patients who have:
    - A history of previous (more than 4 weeks) MI and **either:**
        - Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the NYHA functional classification of HF), **and**
        - Nonsustained VT on Holter (24-hour ECG) monitoring, **and**
        - Inducible VT on electrophysiologic (EP) testing
    - **or:**
        - Left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the NYHA functional classification of HF) **and**
        - QRS duration of equal to or more than 120 ms
3. A familial cardiac condition with a high risk of sudden death, including long QT syndrome, HCM, Brugada syndrome or arrhythmogenic right ventricular

dysplasia (ARVD), or have undergone surgical repair of congenital heart disease.

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult(248)

ACC and AHA provide the following guidance pertaining to the use of ICDs in patients with HF:

1. ICD placement is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year.
2. ICD placement might be considered in patients without HF who have nonischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year.
3. It is reasonable to prescribe amiodarone to decrease recurrence of atrial arrhythmias and to decrease recurrence of ICD discharge for ventricular arrhythmias.

ACC/AHA note that although ICDs are highly effective in preventing death due to ventricular tachyarrhythmias, frequent shocks from an ICD may lead to a significant reduction in QOL. ACC/AHA also note that ICDs have the potential to aggravate heart failure and may be associated with an increase in heart failure hospitalizations. Thus, a decrease in the incidence of sudden death resulting from implantation of an ICD in an individual with heart failure does not necessarily translate into decreased total mortality. Futhermore, decreased total mortality does not guarantee a prolongation of survival with meaningful QOL.

ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices

Guidelines from ACC, AHA, and the North American Society for Pacing and Electrophysiology (NASPE) discuss the use of ICDs in two contexts: 1) as a secondary preventative measure against SCD in patients who have experienced near-fatal arrhythmias, and 2) as a primary preventative measure for protecting against sudden death in patients at high risk for a fatal arrhythmic event. ACC/AHA/NASPE also discuss the contraindications for ICD implantation.

ICDs and Secondary Prevention of Cardiac Arrest or Sustained VT

1. *CAD*: ACC/AHA/NASPE note that patients with coronary artery disease represent the majority of patients receiving devices in most published reports. In addition, ICD implantation is widely accepted as improving the outcome of these patients. ACC/AHA/NASPE also note that patients with reduced LV function may experience greater benefit with ICD therapy than with drug therapy.
2. *Idiopathic DCM:* ACC/AHA/NASPE note that ICD implantation may be preferred for treatment of patients with ventricular tachyarrhythmias or VF and idiopathic DCM.
3. *LQTS:* ACC/AHA/NASPE recommends ICD implantation in selected patients with LQTS in whom recurrent syncope, sustained ventricular arrhythmias, or SCD occurs despite drug therapy. Furthermore, ACC/AHA/NASPE suggest that ICDs should be considered as a primary therapy in certain patients, such as those in whom aborted SCD is the initial presentation of the LQTS, where there is a strong family history of SCD, or when compliance or intolerance to drugs is a concern.
4. *Idiopathic VF:* It has been estimated that in 10% of young patients resuscitated from cardiac arrest, the origin of VF is not determined despite extensive evaluation. ACC/AHA/NASPE note that limited clinical data support the use of ICDs in such patients.
5. *Idiopathic VT:* VT may arise in structurally normal hearts from the right ventricular outflow tract or the LV. ACC/AHA/NASPE recommend that these arrhythmias be treated pharmacologically or with catheter ablation, if amenable, before an ICD is considered for these patients.
6. *HCM:* ACC/AHA/NASPE point out that HCM is often identified as the cause of sudden death in young people, including trained athletes. Ventricular tachyarrhythmias are a common mechanism of sudden death in this condition. Sudden death may also be the first manifestation of the disease in a previously asymptomatic individual. ACC/AHA/NASPE suggests that ICDs may have a role to play in the prevention of sudden death in high risk individuals with this condition. According to ACC/AHA/NASPE, the most prominent characteristics of patients with hypertrophic cardiomyopathy who may be at high risk for experiencing sudden death include the following: 1) prior cardiac arrest or sustained VT; 2) a history of a first-degree relative who has experienced sudden cardiac death; 3) left ventricular hypertrophy with a wall thickness greater than 30 mm; 4) syncope, if exertional, repetitive, or in a young patient if no other cause is documented; and 5) nonsustained

ventricular tachyarrhythmias on ECG monitoring if frequent, repetitive, and prolonged.

7. *Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy:* ACC/AHA/NASPE note that arrhythmogenic right ventricular dysplasia can be an important cause of congestive heart failure and ventricular arrhythmias in some patients. Drug therapy is often used as primary therapy but is often found to be ineffective. Nonpharmacologic options for treatment of significant arrhythmias include catheter ablation of the sites of tachycardia, surgical disarticulation of the right ventricle, and ICDs. In patients with drug refractory malignant arrhythmias, the ICD provides prophylaxis against syncope due to hemodynamically unstable VT and sudden death.
8. *Syncope with Inducible Sustained VT:* ACC/AHA/NASPE note that patients with syncope of undetermined etiology in whom clinically relevant VT/VF is induced at electrophysiologic study may be candidates for ICD therapy. ACC/AHA/NASPE note that the induced arrhythmia observed in these patients is presumed to be the cause of syncope. According to ACC/AHA/NASPE, cardiovascular mortality averages 20% annually, with a large proportion of it sudden. In some patients, antiarrhythmic treatment is limited by inefficacy, intolerance, or noncompliance. ICD therapy has been used in sustained VT populations with comparable results. In patients with hemodynamically significant and symptomatic inducible sustained VT, ICD therapy can be a primary treatment option. The documentation of appropriate ICD therapy of VT and VF from the review of event counters and stored electrograms in such patients lends support to ICD therapy use as a primary treatment option in those who have experienced syncope.

ICDs and Primary Prevention of Sudden Cardiac Death

1. *CAD:* ACC/AHA/NASPE note that electrophysiologic testing has identified a subgroup of individuals with CAD and inducible sustained ventricular tachyarrhythmias that is at high risk for sudden death. While arrhythmia-related symptoms and repeated MIs may help identify such patients, asymptomatic post-MI may also be an important risk factor for sudden death. ACC/AHA/NASPE note that evidence exists that demonstrates improved survival following implantation of an ICD in patients with inducible and nonsuppressible ventricular tachyarrhythmias when compared to conventional drug therapy. ACC/AHA/NASPE also note that evidence exists to show that ICDs reduce mortality among patients with low EF, nonsustained VT on Holter monitoring, and inducible sustained ventricular tachyarrhythmias during electrophysiologic study. ACC/AHA/NASPE state that additional risk

stratification studies are needed to better define which patient subgroups will benefit more or less from ICD therapy.

2. *Following Coronary Artery Bypass Surgery:* Routine ICD insertion does not improve survival in patients with CAD undergoing bypass surgery who are believed to be at high risk of sudden death based on QRS duration and severe LV dysfunction. In one randomized study, no benefit was noted over placebo in patients with EFs less than 35% and a positive signal-averaged ECG who were undergoing surgical revascularization.
3. *As a Bridge to Heart Transplantation:* Orthotopic heart transplantation has emerged as an acceptable therapeutic alternative for selected patients with CHF caused by severe ventricular dysfunction. About 20% of patients requiring transplantation die awaiting a donor organ, with a significant incidence of sudden death. ICDs have been associated with a lower risk of sudden death in these patients. This benefit is diluted by mortality due to heart failure in some patients.
4. *Other high-risk populations:* Other high-risk populations under study for similar benefits include asymptomatic patients—from the standpoint of ventricular tachyarrhythmias—who have impaired LV systolic function and CHF or idiopathic DCM. However, no recommendations can yet be made with respect to these patients owing to insufficient data. Randomized trials of the ICD are ongoing in these populations. Patients with advanced structural heart disease and syncope of unknown origin may benefit from an ICD even if electrophysiologic evaluation is negative.

Contraindications and Limitations of ICD Therapy

1. ICD therapy is not recommended for patients in whom a reversible triggering factor for VT/VF can be definitely identified, such as ventricular tachyarrhythmias in evolving acute myocardial infarction (AMI) or electrolyte abnormalities.
2. ICD therapy is not routinely recommended in coronary disease patients without inducible or spontaneous VT undergoing routine coronary bypass surgery or patients with Wolff-Parkinson-White syndrome who present with VF secondary to atrial fibrillation. Such patients should undergo catheter or surgical ablation if their accessory pathways are amenable to such treatment.
3. Patients with terminal illnesses, NYHA class IV drug refractory CHF who are not candidates for cardiac transplantation, or with a life expectancy not exceeding six months are likely to obtain limited benefit—if any—from ICD therapy. Thus, ICD therapy is discouraged in such individuals.

4. A history of psychiatric disorders, including uncontrolled depression and substance abuse that interfere with the meticulous care and follow-up needed by these patients, is a relative contraindication to device therapy. This is because significant behavioral disorders related to the ICD therapy, including anxiety, device dependence, or social withdrawal, have been described.
5. Patients who have frequent tachyarrhythmias that may trigger shock therapy, such as sustained VT not responsive to antitachycardia pacing or pharmacologic therapy, are not suitable candidates for a device. These events would cause frequent device activation and multiple shocks.

Concerns Related to ICDs and Driving

Despite the fact that ICDs have been shown to be effective in preventing sudden death resulting from cardiac arrhythmia, there is legitimate concern about the consequences of allowing individuals with an ICD to drive. These concerns include the following: 1) ICDs, while effective, do not completely eliminate the risk for SCD. 2) Even the rapid intervention of an ICD following the onset of an arrhythmia may not be enough to protect against driving impairment since sudden incapacitation resulting from syncope may still occur. 3) ICD discharges, whether appropriate or not, may startle or temporarily incapacitate the patient and thereby disrupt safe motor vehicle operation. These concerns are evidenced by the fact that a number of professional bodies recommend that ICD recipients have their private motor vehicle driving privileges restricted and that they not be permitted to drive large trucks or buses (see *Guidelines and Standards Pertaining to ICDs and Driving* above). Indeed, these recommendations have been acted on by many driving licensing agencies that have disqualified recipients of ICDs from driving large trucks and buses and have imposed tight restrictions on private motor vehicle drivers. For example, the U.K. Driver and Vehicle Licensing Agency prohibits private motor car license holders from driving for six months after implantation of an ICD when there have been preceding symptoms of an arrhythmia. Furthermore, if a shock is delivered by the ICD within this six-month period, driving is withheld for a further six months. Any change in device programming or antiarrhythmic drugs triggers a one-month driving prohibition period and all patients must remain under regular review. All individuals in the United Kingdom with an ICD are permanently disqualified from driving a truck or a bus.

Incidence of Sudden Death among Individuals with an ICD

While implantation of an ICD may reduce the risk of sudden arrhythmic cardiac death, it does not cure the underlying condition causing arrhythmia. As noted above, even with an ICD implanted, arrhythmia and SCD may still occur. Table 61 provides a summary of the number of individuals with an ICD who died (all-cause mortality and SCD rates) during follow-up in 26 studies of the effectiveness and safety of ICDs.

Table 61. All-Cause Mortality and Sudden Death Rates among Individuals with an ICD

Reference	Year	N =	Follow-up Time (months)	Overall Death Rate Number of Deaths (%)	Sudden Cardiac Deaths Number of Deaths (%)	Risk Factors for Sudden Cardiac Death
Bardy et al.(227)	2005	829	45 ±NR	182 (22.0)	NR	Number of sudden deaths not reported - NA
Capoferri et al.(249)	2004	100	20 ±10	5 (5.0)	0 (0.0)	No sudden deaths - NA
Hohnloser et al.(228)	2004	332	30 ±13	62 (18.7)	12 (3.6)	NR
Kadish et al.(229)	2004	229	29 ±14	28 (12.2)	3 (1.3)	NR
Nademanee et al.(250)	2003	37	36	0 (0.0)	0 (0.0)	No sudden deaths - NA
Garcia-Moran et al.(251)	2002	38	28 ±15 Range: 4 to 61	6 (15.8)	0 (0.0)	No sudden deaths - NA
Bansch et al.(233)]	2002	54	22.8 ±4.3	1 year: 4 (7.4) 2 years: 92%* 4 years: 86%* 6 years: 73%*	1 year: 0 (0.0) Overall: NR	No sudden deaths - NA
Moss et al.(232)	2002	742	20 ±NR Range: 6 days to 53 months	105 (14.2)	NR	Number of sudden deaths not reported - NA
Freedberg et al.(252)	2001	125	408 ±321 days Range: 1 to 1,277 days	3 (2.4)	0 (0.0)	No sudden deaths - NA
Connolly et al.(230,231)	2000	310	36 ±NR	83 (26.8)	30 (9.7)	NR
Kuck et al.(234,235)	2000	99	57 ±34	36 (36.4)	13 (13.3)	NR
Maron et al.(253)	2000	128	37 ±NR	2 (1.5)	2 (1.5)	NR
Buxton et al.(236-238)	1999	161	Median: 29 Range: NR	35 (21.7)	12 (7.5)	NR
Ruppel et al.(254)	1998	40	23 ±11 Range: 1 to 45	6 (15.0)	0 (0.0)	NA
AVID Investigators(239)	1997	507	18.2 ±12.2	80 (15.8)	NR	Number of sudden deaths not reported
Bigger et al.(240)	1997	446	32 ±16	30-day mort: 24 (5.4) Overall: 101 (22.6)	NR	Number of sudden deaths not reported
Moss et al.(241)	1996	95	27 ±NR Range: <1 to 61	15 (15.8)	NR	Number of sudden deaths not reported
Wever et al.(242)	1995	29	27.0 ±NR Range: 3 days to 56 months	4 (13.8)	1 (3.5)	NR

Reference	Year	N =	Follow-up Time (months)	Overall Death Rate Number of Deaths (%)	Sudden Cardiac Deaths Number of Deaths (%)	Risk Factors for Sudden Cardiac Death
Grimm et al.(255)	1993	241	22 ±22	1 year: 84%* 2 years: 62%* 3 years: 57%*	1 year: 97%* 2 years: 89%* 3 years: 83%*	LVEF ≤30%
Hook et al.(256)	1993	48	15.1 ±7.8	0 (0.0)	0 (0.0)	No sudden deaths - NA
Gross et al.(257)	1991	1,281	NR±NR Range: 0 to 60	231 (18.3) 1 year: 89%* 3 years: 76%* 5 years: 64%*	71 (5.5) 1 year: 96%* 3 years: 92%* 5 years: 87%*	Experienced a shock following implantation
Kou et al.(258)	1991	180	16 ±12	NR	3 (1.7)	NR
Levine et al.(259)	1991	197	9.1 ±11.1	82 (41.6)	NR	Number of sudden deaths not reported - NA
Maloney et al.(260)	1991	105	13 ±8	NR	1 (0.95)	NR
Tchou et al.(261)	1991	184	24.0 ±18.7	29 (15.8)	5 (2.7)	NR
Fogoros et al.(262)	1989	65	25 ±21	NR	1 (1.5)	NR

* Actuarial survival rates
NA Not applicable.
NR Not reported.

The data presented in Table 61 show that although individuals with an ICD may demonstrate improved survival when compared to individuals without such a device. SCD still occurs in a significant proportion of individuals, with observed SCD rates ranged from 0% to 17% (depending on study follow-up time).

The Incidence of Syncope among Individuals with an ICD

Table 62 provides a summary of the number of individuals with an ICD who experienced syncope during follow-up in eight studies that evaluated the effectiveness and safety of ICDs.

Table 62. Number of Individuals with an ICD who Experienced Syncope

Reference	Year	N =	Follow-up (Months)	Number Experiencing Syncope (%)	Survival Free of Syncope	Risk Factors for Higher Syncope Rates
Garcia-Moran et al.(251)	2002	38	28 ±15 Range: 4 t0 61	3 (7.9%)	NR	None identified
Bansch et al.(263)	1998	421	26 ±18	62 (14.7)	12 months: 90% 24 months: 85% 36 months: 81%	1. Low baseline LVEF 2. Induction of fast VT (CL <300 ms) during programmed ventricular stimulation 3. Chronic AF
Trappe et al.(264)	1998	291	38 ±26 Range: <1 to 124	17/224 of patients who were shocked events accompanied by syncope	NR	1. Low baseline LVEF

Reference	Year	N =	Follow-up (Months)	Number Experiencing Syncope (%)	Survival Free of Syncope	Risk Factors for Higher Syncope Rates
Schoels et al.(265)	1995	101	19.3 ±10.5	12 (11.8)	NR	None identified Risk of recurrence of event low in patients syncope free for 9 months or more
Wever et al.(242)	1995	29	27.0 ±NR Range: 3 days to 56 months	1 (3.5)	NR	None identified
Kou et al.(258)	1991	180	16 ±12	13 (7.2)	NR	None identified – looked at age, sex, history of syncope, LVEF, electrophysiologic findings, rate of VT, AADs, and type of ICD
Axtell et al.(266)	1990	184	NR	15 (8.2)	NR	None identified
Fogoros et al.(262)	1989	65	25 ±21	11 (16.7%) shock events accompanied by syncope	NR	None identified

AADs Antiarrthymia drugs.
AF Atrial fibrillation.
CL Cycle length.
ICD Implantable cardioverter defibrillator.
LVEF Left ventricular ejection fraction.
NR Not reported.
VT Ventricular tachycardia.

The data presented in Table 62 demonstrate that, while individuals with an ICD may experience a reduction in the number of episodes of syncope experienced when compared to individuals who do not have such a device implanted, syncope still occurs in a significant proportion of individuals. Depending on the follow-up time of the study, between 3.5% and 19% experienced at least one episode of syncope. Bansch et al.(263) found that the risk for recurrent syncope was highest in the first year (10% of included individuals experienced syncope), but the risk of syncope recurrence was still high in the second and third years after ICD implantation (5% and 4% of enrolled individuals experienced syncopal recurrence in the second and third year of follow-up, respectively).

Bansch et al. used the findings of their study to predict the number of extra crashes one might expect to see among individuals with an implanted ICD if the only restriction on them was that they could not drive if syncopal recurrence occurred.[26] These findings are presented in Table 63. The reader should note that the formula

[26] These authors used the formula: $IR = TD \times V \times SCI \times Ac$. Where, TD=time behind wheel; V=constant (0.28 for private driving and 1.0 for a commercial driving), SCI=risk of unconsciousness; Ac=the underlying risk for a fatal or injurious accident (0.02).

used to predict crash risk has not been validated with actual crash data. Also, the study of Bansch was retrospective and suffers from a number of weaknesses that limit the validity of their estimates of syncope recurrence rates. Consequently, the estimates presented in Table 63 should not be considered as providing accurate crash risk predictions. Only actual crash data collected prospectively from individuals with ICD implants as part of a well designed and executed study can be considered as reliable.

Table 63. Bansch's Predictions of Crash Incidence among ICD Implantees

Driver Population	Crash Incidence in Fatal or Injurious Crashes/100,000 Person-years		
	Year 1	Year 2	Year 3
Private	2.3	1.2	0.9
Commercial	50	25	20

While few studies have reported on risk factors predictive of syncopal recurrence, some risk factors have been identified. These include low baseline LVEF (≤35%), induction of fast VT during programmed ventricular stimulation, chronic arterial fibrillation, and an episode of syncope close to the time of ICD implantation.

Incidence of Shocks (Appropriate or Not) among Individuals with an ICD

Table 64 provides a summary of the number of individuals with an ICD who experienced an ICD shock during follow-up in 21 studies that evaluated the effectiveness and safety of ICDs.

Table 64. Occurrence of ICD Shocks (Appropriate or Not) During Follow-up

Reference	Year	N =	Follow-up (Months)	% of Individuals Shocked at Least Once	% of Shocks Appropriate	Risk Factors for Likelihood of Shock
Sanchez et al.(267)	2006	105	21.8 ±13.7	NR	21.0*	Smoking status
Bardy et al.(227)	2005	829	45 ±NR	31.2	68.3	NR
Capoferri et al.(249)	2004	100	20 ±10	NR	55.0*	NR
Nademanee et al.(250)	2003	37	36	NR	19.4*	NR
Garcia-Moran et al.(251)	2002	38	28 ±15 Range: 4 t0 61	NR	% of total sample who received appropriate shock: 44.7 Year 1: 20%† Year 2: 42.0†	NR

Reference	Year	N =	Follow-up (Months)	% of Individuals Shocked at Least Once	% of Shocks Appropriate	Risk Factors for Likelihood of Shock
Freedberg et al.(252)	2001	125	408 ±321 days Range: 1 to 1,277 days	46.0	NR	LVEF ≤25% Presenting with SMVT rather than cardiac arrest Concurrent use of AADs (Latter not significant risk factor in age and gender adjusted multivariate analysis)
Maron et al.(253)	2000	128	37 ±NR	NR	22.7*	NR
Ruppel et al.(254)	1998	40	23 ±11	57.0	45.4	None identified – looked at age, sex, cardiac disease, and LVEF
Trappe et al.(264)	1998	291	38 ±22 Range: 1 to 124	77.0	NR	None identified - Multivariate analysis included age, gender, underlying disease, LVEF, spontaneous arrhythmias before ICD implant, induced arrhythmias during the electrophysiology study, defibrillation threshold, antiarrhythmic drugs, other drugs (digitalis, diuretics, ACE inhibitors, nitrates), type of implanted device (monophasic or biphasic waveform shocks, ICD with or without antitachycardia pacing modalities).
Conti et al.(268)	1997	82	5 ±1.2	63.0	NR	NR
Freedberg et al.(269)	1995	145	18.3 ±11.7	30.0	NR	NR
Wever et al.(242)	1995	29	27.0 ±NR Range: 3 days to 56 months	62.0	89.0	NR
Finch et al.(270)	1993	40	Range: 1 to 36	65.0	NR	NR
Grimm et al.(255)	1993	241	26 ±22	Total: 42.0 Year 1: 15.0† Year 2: 51.0† Year 5: 76.0†	% of total sample who received appropriate shock: 9.5 Year 1: 13.0† Year 2: 42.0† Year 5: 63.0†	LVEF ≤30% only predictor for earlier shock.
Hook et al.(256)	1993	48	15.1 ±7.8	60.4	73.3	NR
Gross et al.(257)	1991	1,281	0 – 60	1 year: 31%† 3 years: 49%† 5 years: 62%†	NR	NR
Kou et al.(258)	1991	180	16 ±12	58.9	NR	NR

Reference	Year	N =	Follow-up (Months)	% of Individuals Shocked at Least Once	% of Shocks Appropriate	Risk Factors for Likelihood of Shock
Maloney et al.(260)	1991	105	13 ±8	44%	75%	NR
Tchou et al.(261)	1991	184	24 ±18.7	NR	37.0	NR
Axtell et al.(266)	1990	184	NR	NR	38.6	None identified – Factors assessed NR
Fogoros et al.(262)	1989	65	25 ±21	Year 1: 43.0† Year 2: 51.0† Year 3: 71.0† Year 4: 81.0†	Year 1: 28.0† Year 2: 33.0† Year 3: 50.0† Year 4: 64.0†	Lower LVEF

* % of patients who received an appropriate shock
† Actuarial survival rate
AAD Antiarrhythmia drugs.
ACE Angiotensin-converting-enzyme.
ICD Implantable cardioverter defibrillator.
LVEF Left ventricular ejection fraction.
NR Not reported.
SMVT Sustained monomorphic ventricular tachycardia.

Estimates of the number of individuals who will experience ICD discharge (appropriate or inappropriate) vary according to the follow-up time of the study. However, cumulative time-to-first event data from several studies suggests that the majority of individuals with an ICD will experience a shock within the first three years following implantation.(255,257,262) Although estimates vary, the available data suggests that shock is most likely within the first year following implantation (between 15% and 43%). By the second year one should expect that up to half of individuals with an implant will have experienced an ICD discharge at least once. By the end of the third year following implantation, between 60% and 70% of individuals will have experienced at least one shock.

Data on the risk factors that predict who most likely experience an ICD shock and how soon after implantation this event will occur is scarce. The limited available data suggests that the primary predictors for likelihood of ICD shocks are the same primary predictors of who will experience ventricular arrhythmia (i.e., lower LVEF) following implantation of an ICD. Predictors of which individuals will likely receive an inappropriate shock are not clear at this time.

It might be argued that individuals who drive are less sick than those who do not, and are thus less likely to experience the same rate of shocks as those who do not drive. To address this issue, Trappe et al.(264) compared shock rates among individuals who drove and those who did not. These investigators found that the proportion of individuals who experienced at least one ICD shock over a follow-up period of 38 months did not differ between drivers and nondrivers.

Identification of Evidence Base

To address Key Question 4 we looked for data from any source on the incidence of sudden death, sudden incapacitation due to syncope, and ICD discharge during driving. Our inclusion criteria were liberal. The only restrictions that we set on study design were that the study must have reported on the experience of at least 10 individuals and that these individuals represent a reasonable sampling of individuals who will typically receive an ICD. Case reports and series of carefully selected patients chosen to demonstrate a particular point were excluded.

The process through which the evidence base for Key Question 4 was identified is summarized in Figure 2. Our searches[27] identified a total of 427 articles that appeared relevant to this key question. Following application of the retrieval criteria[28] for this question, 69 full-length articles were retrieved and read in full. Of these 69 retrieved articles, 7 were found to meet the inclusion criteria[29] for Key Question 4. Table D-4 of Appendix D lists the 62 articles that were retrieved but then excluded and provides a reason for their exclusion. Table 65 lists the 7 articles that met the inclusion criteria for Key Question 4. Complete descriptions of each of the studies included in this evidence base are presented in the Study Summary Tables that comprise Appendix G.

[27] See Appendix A for search strategies.

[28] See Appendix B for retrieval criteria.

[29] See Appendix C for inclusion criteria.

Figure 22. Development of Evidence Base for Key Question 4

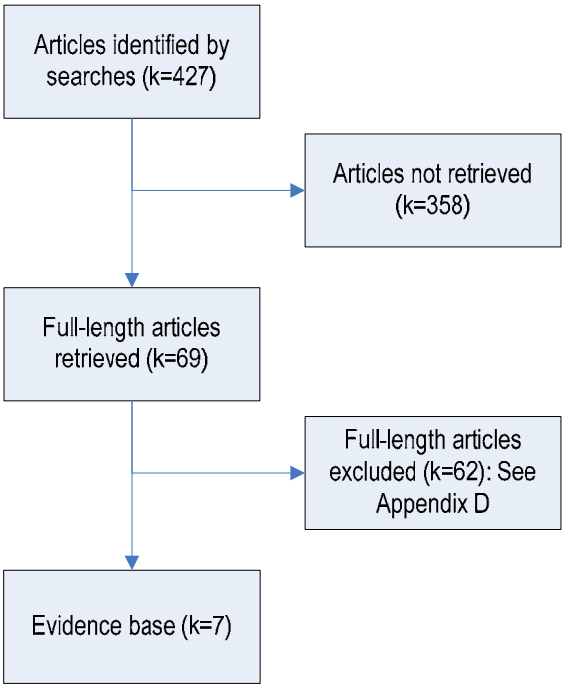


Table 65. Evidence Base for Key Question 4

Reference	Year	Study Location	Country
Akiyama et al.(271)	2001	Subgroup of participants in AVID (Antiarrhythmics versus Implantable Defibrillators) trial, Multicenter	USA
Trappe et al.(264)	1998	University Hospital Herne, Herne	Germany
Conti et al.(268)	1997	University of Florida, Gainesville, Florida	USA
Finch et al.(272)	1997	University of South Carolina, South Carolina	USA
Craney and Powers(273)	1995	Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania	USA
Curtis et al.(274)*	1995	Survey of 742 sites across USA	USA
Finch et al.(270)	1993	University of South Carolina, South Carolina	USA

* Study later excluded for reasons of extremely poor quality (see below)

Evidence Base

This subsection provides a brief description of the key attributes of the seven included studies that examined the impact of ICDs on driving. Here we discuss applicable information pertaining to the quality of the included studies and the

generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 66.

Table 66. Key Study Design Characteristics of Studies that Assessed Impact of ICDs on Driving

Reference	Year	Design	ICD Device(s)	Comparison	Driving exposure considered?	Follow-up Time: months ±SD
Akiyama et al.(271)	2001	Randomized Controlled Trial* Subpopulation of patients enrolled in AVID trial (RCT) between June 1, 1993 and April 7, 1977	Various devices: • Guidant/CPI (St. Paul, MN, USA) • Sulzer Intermedics (Angleton, TX, USA) • Medtronic (Minneapolis, MN, USA) • Ventritex (Sunnyvale, CA, USA).	ICD versus pharmacotherapy.	No	38 ±26
Trappe et al.(264)	1998	Survey	NR	None	No	38 ±26 Range: <1 to 124
Conti et al.(268)	1997	Survey	NR	All had CVD. Those who crashed versus those who did not.	Yes	Crashers: 6 ±1.3 years Noncrashers: 4 ±1.5 years
Finch et al.(272)	1997	Survey	52.4%: 2nd Generation 47.6%: 3rd Generation	None	No	
Craney and Powers(273)	1995	Survey	NR	None	No	26 ±NR Range: 6 to 108
Curtis et al.(274)	1995	Survey	NR	None	No	NR
Finch et al.(270)	1993	Survey	NR	None	No	

* For purposes of addressing this question, this study must be considered as a retrospective survey.

AVID Antiarrhythmics versus implantable defibrillators trial.
CVD Cardiovascular disease.
ICD Implantable cardioverter defibrillator.
NR Not reported.
RCT Randomized controlled trial.
SD Standard deviation.

Quality of Evidence Base

The quality of each of the seven articles included in the evidence base for this key question was assessed using ECRI Quality Scale VI, which was designed specifically for the assessment of the validity of surveys (Appendix H). The findings of our assessment of study quality are presented in Table 67.

Table 67. Quality of Evidence Base for Key Question 4

Reference	Year	Quality Scale Used	Quality Score	Quality
Akiyama et al.(271)	2001	ECRI Quality Scale VI: Surveys	6.2	Low

Reference	Year	Quality Scale Used	Quality Score	Quality
Trappe et al.(264)	1998	ECRI Quality Scale VI: Surveys	5.4	Low
Finch et al.(272)	1997	ECRI Quality Scale VI: Surveys	6.2	Low
Conti et al.(268)	1997	ECRI Quality Scale VI: Surveys	6.2	Low
Craney and Powers(273)	1995	ECRI Quality Scale VI: Surveys	5.4	Low
Curtis et al.(274)	1995	ECRI Quality Scale VI: Surveys	4.2	Extremely Low
Finch et al.(270)	1993	ECRI Quality Scale VI: Surveys	6.2	Low

The quality of the evidence currently available to address Question 4 is low. One study (Curtis et al.(274)) was deemed to be of extremely low quality. Extremely low-quality studies are considered by ECRI to be fatally flawed and should not be allowed to remain in the evidence base. As a consequence, we do not consider outcome data from this study any further in this evidence report. However, because Curtis et al.(274) is commonly cited as providing evidence that individuals with ICDs are at a relatively low risk for a motor vehicle crash, we felt it important to discuss its shortcomings.

Curtis and colleagues surveyed 742 physicians in the United States who were known to be involved in ICD implantation and follow-up. Physicians were questioned about the number of patients followed up, the number of fatal and nonfatal crashes that occurred over a 12-year period, and the recommendations given to the patient regarding driving. Sixty-one percent (61%) of physicians responded to the survey. Such a study cannot provide accurate data on crashes and the causes of those crashes, the number of shock events, or the number of individuals experiencing syncope.

Why were the remaining included studies rated as "Low" quality? The remaining studies were determined to be low quality for a number of reasons.

- All of the included studies used surveys to obtain information pertinent to the key question addressed in this section of the evidence report. A problem inherent to patient surveys is that they are not objective and they rely on the recollections and honesty of the respondents. Furthermore, they rely on the fact that those individuals who are being surveyed are capable of

responding in the first place. In other words, individuals who have died or are incapacitated cannot participate in the survey. In such cases, investigators either count these individuals as nonresponders or they attempt to attain relevant information from friends or relatives. Neither approach is acceptable. First, those who are dead or incapacitated are likely to be a subgroup of individuals who are most at risk for sudden-death or incapacitation while driving. Second, the recollection of details from third parties pertaining to the ICD-related experiences of individuals with an ICD are likely highly questionable.

- The value of the data reported by some of the included studies is limited by high nonresponse rates (Table 68). For example, Akiyama et al. surveyed individuals who had been randomized to receive an ICD or antiarrhythmic drugs a part of the Antiarrhythmics versus Implantable Defibrillators (AVID) trial. Driving surveys were sent to 909 of the 1016 individuals enrolled in the trial. One hundred seven individuals had died before the survey had been sent out. No attempt was made to determine driving history of these 107 individuals from third parties. Seven hundred fifty-eight of the 909 individuals (83%) who were sent a survey responded. Thus, the value of the outcome data reported from this study is limited by a high attrition rate (total attrition = 25%).

Table 68. Survey Response Rates Achieved by Included Studies

Reference	Year	Number of Potential Survey Subjects	Number Actually Surveyed (%)
Akiyama et al.(271)	2001	1,016	758 (75%)
Trappe et al.(264)	1998	410	291 (71%)
Conti et al.(268)	1997	82	82 (100%)
Finch et al.(272)	1997	?	105 (?)
Craney and Powers(273)	1995	100	97 (97%)
Finch et al.(270)	1993	40	40 (100%)

Generalizability of Evidence to Target Population

In this small group of studies subjects were generally male but older than would be expected for the average CMV driver. Driving distances were not addressed in these studies; however, a number of other papers indicated that most ICD recipients discontinued driving, drove fewer miles, or modified their driving habits in some way by not driving in inclement weather, avoiding peak traffic and engaging in similar precautions.

Table 69. Patient Population in Studies that Assess Key Question 4

	Akiyama et al.(271)	Trappe et al.(264)	Conti et al.(268)	Finch et al.(272)	Craney and Powers(273)	Finch et al.(270)
Year	2001	1998	1997	1997	1995	1993
If survey, response rate?	83%	71%	99%	NR	97%	100%
Inclusion Criteria	Patients enrolled on AVID who were alive when first questionnaire was presented (9 months after start of AVID). AVID enrolled cardiac arrest survivors (45%) or sustained VT with syncope, or symptomatic sustained VT (55%) with LVEF <40%.	History of ≥1 documented, recurrent episodes of sustained VT and/or VF refractory to antiarrhythmic drug treatment.	Consecutive patients who had received an ICD at the University of Florida between 1988 and 1993.	Individuals with an ICD implanted at the Medical University of South Carolina who responded to a survey.	ICD implanted >6 months; spoke and understood English; had a telephone in place of residence; not hospitalized at time of interview.	Consecutive patients who had ICD implanted at the Medical University of South Carolina.
Exclusion Criteria	NR	NR	NR	NR	NR	NR
N =	328	241	82	105	97	40
Patients advised not to drive?	Yes For 6 months post-implantation.	Yes All advised never to drive again.	Yes All advised not to drive for at least 6 months.	Yes All advised never to drive again.	Yes All advised never to drive again.	Yes All advised never to drive again.
% Who Resumed Driving	90.0	59.0	89.2	77.0	74.0	70.0
N Drivers =	295	171	73	81	72	28
Mean Age ±SD	NR	57 ±10 Range: 23 to 73	63 ±11	61 ±NR	66.4 ±9.7 Range: 30 to 84	62.7 ±NR Range: NR
% Male	85.6	94.0	NR	79.0	74.2	82.5
Underlying Disease	NR	67% CAD; 19% DCM; 5% R/LVD; 9% Other	NR	NR	NR	NR
Mean LVEF ±SD	32% ±NR	Range: 12 to 85%	NR	36% ±NR Range: 12 to 75%	NR	NR
NYHA	NR	17% NYHA I; 48% NYHA II; 23% NYHA III	NR	NR	NR	NR
% CMV Drivers	NR	NR	NR	NR	NR	NR
Driving Exposure	46% - 50 miles/week and 25% >100 miles/week	14% gave up driving after implant; 31% <30 miles/week; 7.7% 31 to 60 miles/week; 12.9% 61 to 120 miles/week; 7.0% >121 miles/week	Average 16 miles per day	NR	74% >60 miles per week	NR

	Akiyama et al.(271)	Trappe et al.(264)	Conti et al.(268)	Finch et al.(272)	Craney and Powers(273)	Finch et al.(270)
FUT (months)	35 ±NR Range: NR	38 ±26 Range: <1 to 124	5.3 years ±NR Range: NR	21.6 ±NR Range: NR	26 ±NR Range: 6 to 108	NR ±NR Range: 1 to 36

* For the purposes of this report the study is a prospective survey of individuals enrolled in an RCT. Only data from the ICD arm of the study is pertinent to this Evidence Report.

AID Antiarrhythmics versus implantable defibrillators.
CAD Coronary artery disease.
CMV Commercial motor vehicle.
DCM Dialated cardiomyopathy.
FUT Follow-up time.
ICD Implantable cardioverter defibrillator.
LVEF Left ventricular ejection fraction.
NR Not reported.
NYHA New York Heart Association.
R/LVD Right/left ventricle dysplasia.
VF Ventricular fibrillation.
VF Ventricular fibrillation.
VT Ventricular tachycardia.

Findings

In order to address Key Question 4 we considered data pertaining to four outcomes; crash rate, the proportion of individuals who experienced sudden death while driving, the proportion of individuals who experienced syncope while driving, and the proportion of individuals who received at least one shock from their ICD while driving. Not all included studies reported on all of these outcomes (Table 70).

Table 70. Relevant Outcome Data Reported

Reference	Year	Crash Rate*	Crash Rate Following Symptoms of Arrhythmia	% Who Experienced Syncope or Sudden – Cardiac Death While Driving	% Who Received ≥1 Shock from ICD While Driving
Akiyama et al.(271)	2001	✓†	✓†	✓†	✓
Trappe et al.(264)	1998	✓	✓	✓	✓
Conti et al.(268)	1997	✓	✓		✓
Finch et al.(272)	1997	✓	✓	✓	✓
Craney and Powers(273)	1995				✓
Finch et al.(270)	1993	✓		✓	✓
TOTAL STUDIES		**4‡**	**3‡**	**3‡**	**6**

* Primary outcome
† Data presented for entire population of individuals who had experienced life-threatening tachyarrhythmia regardless of whether they had received an ICD or pharmacotherapy-data not appropriate for addressing key question 4
‡ Excludes Akiyama et al.(271)

Motor Vehicle Crash among Individuals with ICD

Four of the six included studies presented data on the number or frequency of crashes that occurred among individuals with an ICD. These data are summarized in Table 71.

Table 71. Crash Data Extracted from Included ICD Studies

Reference	Year	Number of Drivers	Mean FUT ±SD (months)	Number Who Crashed at Least Once (%)	Number of Crashes at Fault (%)	Number of Total Crashes Related to CVD (%)
Trappe et al.(264)	1998	171	38 ±24	11 (6.4)	1 (9.1)	0 (0.0)
Conti et al.(268)	1997	73	5.3 years ±NR	0 (0.0)	0 (0.0)	0 (0.0)
Finch et al.(272)	1997	81	21.6 ±NR	0 (0.0)	0 (0.0)	0 (0.0)
Finch et al.(270)	1993	28	NR ±NR Range: 1 to 36	0 (0.0)	0 (0.0)	0 (0.0)

* Investigators did not present crash data for two groups separately. Rather they reported on the overall number of crashes experienced by individuals treated with an ICD and pharmacotherapy and merely noted that crash rate was lower in ICD group.
CVD Cardiovascular disease.
ICD Implantable cardioverter defibrillator.

NR Not reported.
SD Standard deviation.

Crashes reportedly occurred in only one of the four included studies. Trappe et al. noted that 11 individuals enrolled in their study experienced at least one crash during follow-up. Of these, only one was determined to be the fault of the driver, and none of the crashes were the consequence of either CVD or an event associated with the implanted ICD. No crashes were reported to have occurred among the individuals enrolled in the remaining three studies. This may be the combined consequence of the small size of these studies and their short follow-up times. In order to determine a reliable estimate of the crash rate associated with ICDs, studies with far larger sample sizes and longer follow-up times will need to be performed.

Occurrence of Syncope and Sudden Death while Driving

Three of the six included studies for Key Question 4 reported on the occurrence of syncope and sudden death while an individual with an ICD was driving. Relevant data from these studies are summarized in Table 72.

Table 72. Number of Individuals who Experienced Syncope or SCD while Driving

Reference	Year	N =	Number of Drivers	Mean FUT ±SD	Number who Experienced Syncope (%)	Number Who Experienced Syncope While Driving (%)	Number Who Experienced Sudden-Cardiac Death (%)	Number Who Experienced Sudden-Cardiac Death While Driving (%)
Trappe et al.(264)	1998	241	171	38 ±28 Range: <1 to124	15 (5.2)	0 (0.0)	8 (2.8)	0 (0.0)
Finch et al.(272)	1997	105	81	21.6 ±NR	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Finch et al.(270)	1993	40	28	Range: 1 to 36	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

FUT Follow-up time.
NR Not reported.
SCD Sudden cardiac death.
SD Standard deviation.

None of the individuals enrolled in the three included studies above experienced syncope or SCD while driving.

Occurrence of ICD Discharge while Driving

All six included studies reported on the occurrence of ICD discharge during driving. Relevant data from these studies are summarized in Table 73.

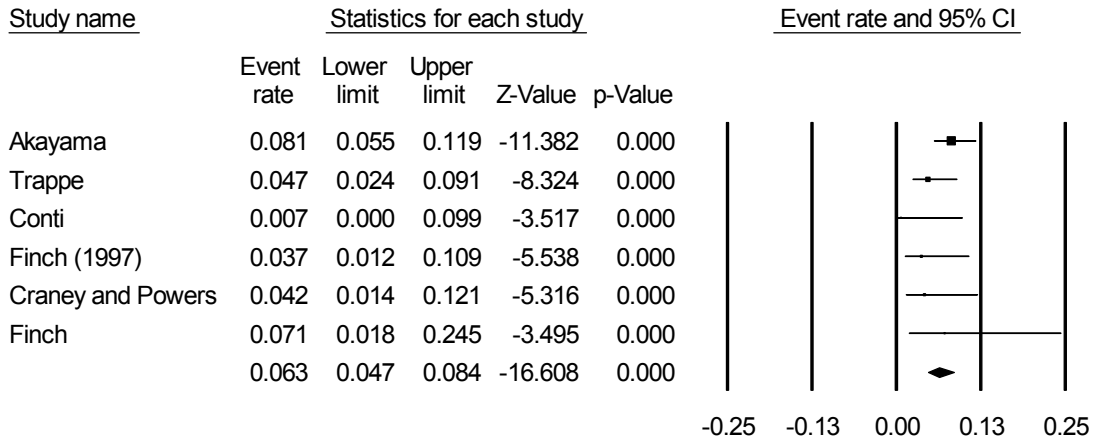
Table 73. Number of Individuals with ICD who Experience Shock while Driving

Reference	Year	N =	Number of Drivers	Mean FUT ±SD	Number Who Experienced Shock During Follow-up (%)	Number Who Experienced Shock While Driving (%)
Akiyama et al.(271)	2001	328	295	35 ±NR Range: NR	NR	24 (8.1)
Trappe et al.(264)	1998	241	171	38 ±28 Range:<1 to124	224 (77.0)	8 (4.7)
Conti et al.(268)	1997	85	73	5.3 years ±NR Range: NR	52 (63.4)	0 (0.0)*
Finch et al.(272)	1997	105	81	21.6 ±NR Range: NR	52 (49.5)	3 (3.7)
Craney and Powers(273)	1995	97	72	26 ±NR Range: 6 to 108	42 (43.3)	3 (4.1)
Finch et al.(270)	1993	40	28	Range: 1 to 36	26 (65.0)	2 (7.1)

* Discharges during previous 12 months only.
FUT Follow-up time.
ICD Implantable cardioverter defibrillator.
SD Standard deviation.

In order to obtain an estimate of the expected proportion of individuals with an ICD who might be expected to experience at least one ICD discharge shock during follow-up, we pooled data from all six studies using meta-analysis. Despite the fact that follow-up times varied across studies, homogeneity testing found that the ICD discharge data were consistent ($Q = 6.516$, $P = 0.259$; $I^2 = 23.268$). Because these data were homogeneous, we pooled them using a fixed-effects model. The results of this analysis are presented in Figure 23. According to the findings of this analysis, the number of individuals with an ICD who will experience at least one shock during driving (appropriate or inappropriate) is in the order of 6.3% (95% CI: 4.7–8.4%). A series of sensitivity analyses found the findings of this analysis to be robust (Figure H-7 through Figure H-11 of Appendix H).

Figure 23. Summary Estimate of Proportion of Individuals Expected to Experience ICD Discharge during Driving



Time to First ICD Discharge while Driving

None of the included studies reported on the time to first ICD discharge during driving. However, Trappe et al.(264) reported on the time interval from ICD implantation to first discharge among drivers and nondrivers. No significant differences among drivers and nondrivers in the interval postimplant to first therapy were observed. The mean time to first ICD discharge was 9 months (SD: 12) and among nondrivers 9 months (SD: 10). First ICD discharge was delivered within the first 6 months postimplant in 52% of drivers and 53% of nondrivers.

Risk Factors for ICD Discharge while Driving

In an attempt to identify individuals who are at most risk for an ICD discharge during driving, Trappe et al.(264) performed a multivariate analysis. This analysis included data about age, gender, underlying disease, LVEF, spontaneous arrhythmias before ICD implant, induced arrhythmias during the electrophysiology study, defibrillation threshold, antiarrhythmic drugs, other drugs (i.e., digitalis, diuretics, ACE inhibitors, nitrates), and types of implanted devices (i.e., monophasic or biphasic waveform shocks, ICD with or without antitachycardia pacing modalities). These investigators were unable to identify any characteristics that could be used to identify individuals who are at most risk for an ICD discharge during driving. None of the remaining included studies

attempted to identify which individuals with an ICD presented the most risk for ICD discharge during driving.

Conclusions

The conclusions of our assessment of the available evidence pertaining to Key Question 4 are as follows:

Whether individuals with an ICD implant experience crash that can be directly attributed to CVD or the ICD implant itself cannot be determined at the present time.

Four of the six included studies presented data on the number or frequency of crashes that occurred among individuals with an ICD. None of these studies compared crash rates occurring among individuals with an ICD to crash rates among individuals without CVD. Consequently, it is not possible to determine whether individuals with an ICD are at increased risk for a motor vehicle crash.

Crashes reportedly occurred in only one of the four included studies. Eleven individuals enrolled in this study experienced at least one crash during follow-up. Of these, only one was purportedly the fault of the driver, and none of the crashes were the consequence of either CVD or an event associated with the implanted ICD. The fact that no crashes reportedly occurred in the remaining studies may be the combined consequence of the small size of these studies and their short follow-up times. In order to determine a reliable estimate of the crash rate associated with ICDs, studies with far larger sample sizes and longer follow-up times will need to be performed.

Whether individuals with an ICD implant experience sudden death or incapacitation during driving cannot be determined at the present time.

Three of the six included studies reported on the occurrence of syncope and sudden death while an individual with an ICD was driving. None of the individuals enrolled in the three included studies above experienced syncope or SCD while driving. Given the fact that syncope and sudden-death while driving have to be considered as being rare events, the fact that no cases were observed in the three included studies cannot be considered as evidence that such events will not occur while driving.

Some individuals with ICD will experience ICD discharge while they are driving (Strength of Evidence: Strong).

- **Quantitative assessment of the available data suggests that approximately 6.3% (95% CI: 4.7–8.4%) of individuals who drive with an ICD will experience an ICD discharge while driving (Stability of Estimate: Low).**

  Six included studies reported on the occurrence of ICD discharge during driving. Five of these six studies reported that ICD discharge had occurred in some individuals while driving. Despite the fact that follow-up times varied across studies, ICD discharge data were remarkably consistent. Pooling of these data found that the number of individuals with an ICD experience at least one shock during driving (appropriate or inappropriate) in the order of 6.3%. A series of sensitivity analyses found the findings of this analysis to be robust.

Key Question 5: What is the risk of sudden death or incapacitation in individuals with low Left Ventricular Ejection Fraction (<50%, <40%, <35%)?

Background

In cardiovascular physiology, ejection fraction (EF) is the fraction of blood pumped out of a ventricle with each heart beat. The term ejection fraction applies to both the right and left ventricles; one can speak equally of the left ventricualr EF (LVEF) and the right ventricular EF (RVEF). Without a qualifier, the term ejection fraction refers specifically to that of the left ventricle (LVEF).

By definition, the volume of blood within a ventricle is known as the end-diastolic volume (EDV). Similarly, the volume of blood left in a ventricle at the end of contraction is end-systolic volume (ESV). The difference between EDV and ESV is the volume of blood ejected with each beat, or stroke volume (SV). EF is the fraction of the EDV that is ejected with each beat; that is, it is SV divided by EDV:

$$E_f = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

In a healthy 70-kg (154 lbs) male, the SV is approximately 70 ml and the left ventricular EDV is 120 ml, giving an EF of 70/120, or 58%. Right ventricular volumes being roughly equal to those of the left ventricle, the EF of the right ventricle is normally equal to that of the left ventricle within narrow limits.

Healthy individuals typically have EFs greater than 0.55. However, normal values depend on the modality being used to calculate the EF. EF is commonly measured by echocardiography, in which the volumes of the heart's chambers are measured during the cardiac cycle. EF can then be obtained by dividing stroke volume by EDV as described above. Other methods of measuring EF include cardiac MRI, fast-scan cardiac computed axial tomography imaging, ventriculography, Gated SPECT, and the MUGA scan. A MUGA scan involves the injection of a radioisotope into the blood and the detection of its flow through the left ventricle. The historic gold standard for the measurement of EF is ventriculography.

Damage to the muscle of the heart (myocardium), such as that sustained during MI or in cardiomyopathy, impairs the heart's ability to eject blood and therefore reduces EF. This reduction in the EF can manifest itself clinically as heart failure (HF). Sudden death is common in patients with chronic heart failure, acute MI, and CAD.(275-278) Risk screening is the first step for primary prevention of sudden death, and should use simple, easily performed measurements. LVEF is considered to be one of the most important predictors of prognosis; those with significantly reduced LVEF typically have poorer prognoses. Low LVEF is recognized as a primary risk factor for sudden death after MI, and from ischemic and nonischemic causes in CHF patients.(275,276) However, it is likely that combined and/or accumulated risk markers may provide more powerful risk stratification for sudden death than LVEF alone.(275,277,279-283)

The purpose of this section is to systematically review the data pertaining to the risk of sudden death or incapacitation in individuals with low LVEF with the aim of informing FMCSA about which individuals with low LVEF are most at risk for sudden death or incapacitation. In attempting to address this issue we searched for studies of any design that attempted to identify risk of sudden death or incapacitation in individuals with low LVEF. These studies included case-control trials, case series, controlled trials, and natural history studies.

Identification of Evidence Base

The identification of the evidence used in this section of the evidence report is presented in Figure 24. Our searches[30] identified a total of 100 articles that appeared relevant. Following application of the retrieval criteria for this question, 20 full-length articles were retrieved and read in full. Ten of these 20 retrieved articles were found to meet our criteria for inclusion[31] (Table 74). Table D-5 of Appendix D lists the 10 articles that were retrieved but then excluded and provides the reason for their exclusion.

Figure 24. Development of Evidence Base for Key Question 5

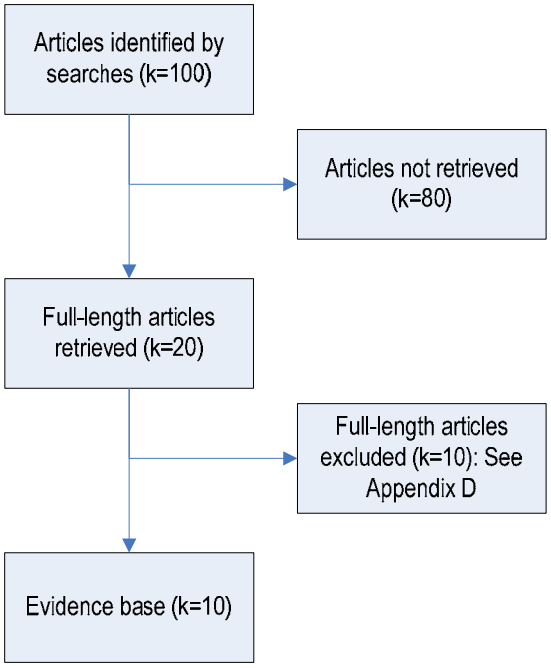


Table 74. Evidence Base

Primary Reference	Year	Study Location	Country
Studies That Used Multiple Levels of LVEF Stratification			
Watanabe et al.(275)	2006	Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine	Japan

[30] See Appendix A for search strategies.

[31] See Appendix C for inclusion criteria.

Primary Reference	Year	Study Location	Country
Solomon et al.(276)	2005	Cardiovascular Division, Brigham and Women's Hospital	USA
Buxton et al.(277)	2002	85 sites in the United States and Canada	USA and Canada
Adachi et al.(279)	2001	Kobe University School of Medicine Hospital	Japan
Sharir et al.(280)	2001	Cedars-Sinai Medical Center	USA
Studies That Did Not Use Multiple Levels of LVEF Stratification			
Pedersen et al.(284)	2006	27 centers in Denmark	Denmark
Balanescu et al.(285)	2004	Cardiology Departments, Bucharest Emergency Hospital and Bucharest University Hospital	Romania
Raczak et al.(281)	2004	Department of Cardiology, Medical University of Gdanska	Poland
La Rovere et al.(282)	2003	Instituto Scientifico di Montescano	Italy
Berger et al.(283)	2002	Heart Failure Center at the Department of Cardiology, University of Vienna	Austria

LVEF Left ventricular ejection fraction.

Evidence Base

This subsection provides a brief description of the key attributes of the 10 studies that met the inclusion criteria for this key question. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Detailed information pertinent to this section that has been extracted from included studies is presented in the Study Summary Tables that can be found in Appendix G.

The primary characteristics of the 10 included studies that address Key Questions 5 and 6 are presented in Table 75. Nine studies were prospective observational studies; one was a retrospective observational study. The studies divided into one of two categories: (1) those that reported risk of sudden death or incapacitation in individuals with low LVEF using multiple levels of LVEF stratification (e.g., LVEF ≤30%, ≤40%, or >40%); and (2) those that reported risk of sudden death or incapacitation in individuals with low LVEF using a single level of LVEF stratification (e.g., LVEF >30%).

Table 75. Key Study Design Characteristics of Studies that Address Key Question 5

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Studies That Used Multiple Levels of LVEF Stratification					
Watanabe et al.(275)	2006	Prospective Observational Study	This study was undertaken to evaluate the use of risk markers for estimating sudden death risk by analyzing the database from a multi-center heart failure registry, CHART (Chronic Heart failure Analysis and Registry).	The CHART study is a multi-center prospective observational study, which included 680 stable chronic heart failure patients who had organic heart disease and a previous history of hospitalization due to clinical congestive heart failure. The CHART study also included symptomatic patients who had not been hospitalized, if they had organic heart disease and LVEF <50% or left ventricular diastolic diameter (LVDD) ≥55 mm. The underlying etiology of CHF was divided into 5 categories, i.e., dilated cardiomyopathy (DCM), coronary artery disease (CAD), valvular heart disease (VHD), left ventricular hypertrophy (LVH), and other heart diseases. Analysis was performed in patients with CAD, DCM, LVH, and corrected VHD, excluding uncorrected VHD and other heart diseases. The mode of death was categorized as heart failure death, sudden death, or noncardiac death. Sudden death was defined as sudden, unexpected death without worsening heart failure. It included witnessed sudden collapse and death, and unwitnessed deaths which were unexpected and could not be explained by noncardiac causes.	Risk markers were evaluated with Cox's proportional hazard model using the stepwise method. The end point was sudden death. The sudden death-free survival rate was estimated by Kaplan-Meier analysis.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Solomon et al.(276)	2005	Prospective Observational Study	This study was undertaken to better delineate the early and later risk of sudden death after myocardial infarction (MI) and the association of these risks with LVEF using patients enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).	VALIANT was a randomized, controlled trial of treatment with valsartan, captopril, or both in 14,703 patients with a first or subsequent acute myocardial infarction (AMI) complicated by heart failure, left ventricular systolic dysfunction, or both. The median duration of follow-up was 24.7 months. Sudden deaths and episodes of cardiac arrest with resuscitation were combined. The LVEF was determined before randomization (a median of 5 days after myocardial infarction (MI)) at the clinical site in 11,256 patients. Deaths were classified as having cardiovascular or noncardiovascular causes, and deaths from cardiovascular causes were further classified as sudden or due to MI, heart failure, stroke, or another cardiovascular cause. Sudden death was explicitly defined as death that occurred "suddenly and unexpectedly" in a patient in otherwise stable condition and included witnessed deaths (with or without documentation of arrhythmia) and unwitnessed deaths if the patient had been seen within 24 hours before death but had not had premonitory heart failure, MI, or another clear cause of death. Cardiac arrest with resuscitation was defined as cardiac arrest from which a patient regained consciousness and subsequent cognitive function, even briefly.	The analysis of the incidence and timing of sudden death included all patients and was related to the LVEF in the subgroup of patients for whom information on the ejection fraction (EF) was available. The rates of sudden death were assessed by dividing the events in each period by the number of person-days of exposure and are expressed as the percentage per month. The risk of sudden death associated with each decrease of 5 percentage points in the LVEF was assessed in a Cox proportional-hazards model, with adjustment for all known baseline covariates.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Buxton et al.(277)	2002	Retrospective Observational Study	The purpose of this study was to evaluate the relation between EF, inducible ventricular tachyarrhythmia, and the modes of death for patients enrolled in MUSTT (Multicenter Unsustained Tachycardia Trial). In addition, the authors sought to provide further information regarding how best to stratify sudden death risk in patients with chronic coronary disease and moderate reductions of EF (30% to 40%) compared with those with severely reduced left ventricular function (EF <30%).	MUSTT was a randomized clinical trial designed to determine whether antiarrhythmic therapy guided by electrophysiologic testing would reduce the risk of sudden death and total mortality in patients with documented CAD, LVEF ≤40%, and asymptomatic nonsustained VT. The authors analyzed the relation of EF and inducible ventricular tachyarrhythmias to mode of death in all 1,791 patients enrolled in the MUSTT who did not receive antiarrhythmic therapy. The authors used a modified Hinkle-Thaler system to classify deaths. Arrhythmic deaths included unwitnessed deaths (if stable when last observed before death), witnessed instantaneous deaths, nonsudden deaths due to incessant tachycardia, sequelae of cardiac arrest, antiarrhythmic drug toxicity, and complications of implanted defibrillators. Deaths of patients with end-stage heart failure or cardiogenic shock were not classified as arrhythmic. Cardiac arrest was defined as sudden loss of consciousness that required DC countershock to restore consciousness or stable blood pressure and rhythm. For analytic purposes, the authors grouped arrhythmic deaths and cardiac arrests together.	Cumulative event rates and survival curves were calculated by the Kaplan-Meier method, and outcome differences were assessed with the Cox proportional hazards model. The authors evaluated the effect of EF on clinical outcomes in 2 ways, namely, treating it as a continuous variable and dichotomizing it at <30% versus ≥30%. As a continuous variable, the authors examined the shape and strength of the relation of EF with mortality and with arrhythmic events using a flexible model-fitting approach that involved cubic spline functions (cubic polynomials). In addition, covariate-adjusted analyses of the effects of inducible tachyarrhythmia and EF on outcomes were performed with the Cox model. To descriptively summarize key relationships, hazard ratios and 95% CIs were calculated with the Cox model. To assess the effects of inducible tachyarrhythmia and EF on mode of death (i.e., on whether or not an event was arrhythmic), two approaches were used. With EF dichotomized, the percentages of deaths/cardiac arrests that were arrhythmic in each of the 4 inducibility/EF groups were tabulated and compared. Additionally, logistic regression analysis was used to jointly assess the relationship of these factors to whether an outcome event was arrhythmic, also taking into account other patient characteristics.
Adachi et al.(279)	2001	Prospective Observational Study	The aim of this study was to evaluate the efficacy of microvolt-level T-wave alternans (TWA) and to compare it with conventional parameters for prospective risk stratification of sudden cardiac death (SCD) in patients with DCM.	Sixty-four patients with DCM underwent assessment of TWA, LVDD, LVEF, signal-averaged ECG, and analysis of 24-h Holter monitoring and QT dispersion (QTd). The endpoint of the study was defined as either SCD or documented sustained ventricular tachycardia/ventricular fibrillation (SVT/VF) during the follow-up period. Sudden death was defined as instantaneous, unexpected death or death within 1 hour of symptom onset not related to circulatory failure. The SVT was defined as a documented tachycardia of ventricular origin at a rate of ≥100 beats/min and lasting for >30 seconds or resulting in hemodynamic collapse.	The cumulative probability of events was determined by the Kaplan-Meier method, and differences in the distribution of events were evaluated with the log-rank test. Significant factors detected by univariate analysis were reassessed by multivariate analysis. Multivariate analysis was performed by means of a Cox regression analysis.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Sharir et al.(280)	2001	Prospective Observational Study	The aim of this study was to determine the value of gated myocardial perfusion SPECT in the assessment of outcome specific (nonfatal MI versus cardiac death (CD)) independent predictors and to examine the value of integrating perfusion and function data in stratifying patients into subsets with low-, intermediate-, and high-risk of CD.	The authors identified 2,686 consecutive patients who underwent separate acquisition, dual-isotope myocardial perfusion gated SPECT (resting ^{201}Tl/stress ^{99m}Tc-sestamibi gated SPECT) and were monitored for >1 year for CD and nonfatal MI. Poststress EF was automatically generated. Events were defined as either CD, as noted and confirmed by review of death certificates and hospital charts or physicians' records, or nonfatal MI, as evidenced by hospital records, indicating the appropriate combination of symptoms, electrocardiography, and creatine phosphokinase myocardial band levels.	Cox proportional hazards regression analysis was applied to determine the independent predictors of CD and nonfatal MI as separate endpoints. Patients were censored at the first event. Kaplan-Meier survival analysis with stratification by EF was performed. Survival curves were compared by the log-rank test. Correlations between the CD rate and EF were evaluated using ANOVA.
Studies That Did Not Use Multiple Levels of LVEF Stratification					
Pedersen et al.(284)	2006	Prospective Observational Study	This study was undertaken to examine the mode of death in patients with a recent MI and atrial fibrillation (AF), to further clarify the cause of the excess mortality observed in several studies, and to examine the risk in prespecified subgroups.	The relation between AF/atrial flutter (AFL) and modes of death were analyzed in 5,983 patients who were discharged alive after hospitalization for an AMI. Survival status was obtained 2 years after screening of the last patient. An independent endpoint committee assessed the modes of death. LVEF was determined in all the screened patients and information about presence or absence of AF/AFL was prospectively collected. SCD was defined as cardiovascular death within 1 hour of onset (or significant worsening) of symptoms leading to death.	LVEF was dichotomized at 40% and the risk ratio was estimated for patients with LVEF <40%, using LVEF ≥40% as the reference.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Balanescu et al.(285)	2004	Prospective Observational Study	This study was designed to assess the 1-year prognostic value of heart rate variability (HRV) parameters for sudden death and total mortality in patients with AMI depending on the administration of reperfusion therapy in the first 12 hours after symptom onset.	The authors included 463 consecutive patients with AMI. Two hundred and eleven were treated by thrombolysis or primary PTCA, the other 252 patients receiving conventional therapy. Time-domain (SDNN, rMSSD) and frequency-domain (LF, HF, total power) HRV parameters were calculated from 24-hour Holter ECG recordings 10-20 days after AMI. The primary endpoint was one-year total mortality and SCD. The secondary endpoints included the recurrence of angina or MI and the occurrence of symptoms of heart failure. SCD was defined as unexpected *exitus* in the first 24 hours after symptom onset related to recurrent MI or documented severe ventricular arrhythmias. General mortality included cardiac and extra-cardiac death of any cause.	Analyses were completed to discern if HRV parameters differed between patients with AMI that were alive at 1 year versus those that had died using the unpaired Student's *t*-test. All risk factors that resulted in significance based on the unvariate analysis were entered in survival analysis using the Cox proportional hazard regression model to assess independent predictors of survival at 1 year after MI. Relative risks of survival status were calculated for each significant parameter. Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank (Cox-Mantel) test for the independent variables that determined mortality. The positive predictive value was calculated as the proportion of patients with a positive test that had died and the negative predictive value as the proportion of patients with a negative test who survived.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
Raczak et al.(281)	2004	Prospective Observational Study	The aim of this study was to evaluate the predictive value of electrophysiologic testing together with noninvasive measurement of baroreflex sensitivity (BRS) in patients surviving a sustained arrhythmic episode.	The study group comprised 112 post-MI patients consecutively referred for electrophysiologic study (EPS) following documented ventricular fibrillation (VF, n = 20), sustained ventricular tachycardia (VT, n = 74) or a syncopal episode with subsequently documented nonsustained VT at Holter monitoring (n = 18). Patients were followed up for a median of 315 days (range: 14–1,126). The endpoint of the study was appropriate and documented ICD discharge for fast VT or VF or sudden (presumably arrhythmic) death, defined as death occurring within 1hour of onset of symptoms in a previously medically stable patient, death during sleep or unwitnessed death occurring within 1hour of the patient last being seen alive.	Survival analysis was performed after categorization of continuous variables (LVEF, BRS, resting RR interval ,and systolic arterial pressure) into 3 levels according to the following rule: each variable was assigned to level 1 (higher risk) if its value was ≤25th percentile, level 2 (intermediate risk) if its value was between the 25th and 50th percentiles, and level 3 (lower risk) for higher values. The other categorical variables considered in the analysis were NYHA class, the location of the previous MI, inducibility of VT and drug therapy; age and sex were considered as covariates (adjusting factors). The univariate predictive value of each variable was assessed by proportional hazards regression analysis. The risks of the different risk classes (low, intermediate and high) were compared statistically and 2 contiguous classes merged together in the case of a nonsignificant difference. All significant univariate predictors and their interactions were analyzed jointly in a multivariate regression model. In case of significant interaction between 2 variables, the analysis was restarted after splitting the data according to the levels of either of them. Results are presented as relative risk (RR) and corresponding 95% CI. Event-free curves were estimated by the Kaplan-Meier method and compared by the log-rank test.

Reference	Year	Study Design	Purpose of Study	Study Details	Method Used to Determine Risk
La Rovere et al.(282)	2003	Prospective Observational Study	This study tested the prognostic information from short-term heart rate variability (HRV) for sudden, presumably arrhythmic death in a large population of patients with moderate to severe chronic heart failure, comparing this in a multivariate model that included many clinical and functional risk predictors.	A multivariate survival model for the identification of sudden (presumably arrhythmic) death was developed with data from 202 consecutive patients referred between 1991 and 1995 with moderate to severe CHF (the derivation sample). Time- and frequency-domain HRV parameters obtained from an 8' recording of ECG at baseline and during controlled breathing (12 to 15 breaths/minute) were challenged against clinical and functional parameters. This model was then validated in 242 consecutive patients referred between 1996 and 2001 (validation sample). The end point of survival analysis was sudden (presumably arrhythmic) death, defined as death occurring within 1 hour of onset of symptoms in a previously medically stable patient, death during sleep, unwitnessed death occurring within 1 hour of the patient last being seen alive, or appropriate and documented ICD discharge for fast VT or VF.	Significant univariate predictors in the same compartment of variables (e.g., echocardiographic, HRV) were analyzed jointly in a multivariate Cox model to identify the subset containing independent prognostic information. All selected variables were then used as candidates for the final survival model. Kaplan-Meier survival curves were compared with the log-rank test.
Berger et al.(283)	2002	Prospective Observational Study	The aim of this study was to test the value of B-type natriuretic peptide (BNP) levels for prediction of sudden death in a large ambulant patient population with a LVEF <35%.	BNP levels, in addition to other neurohormonal, clinical, and hemodynamic variables, were obtained from 452 patients with a LVEF ≤35%. For prediction of sudden death, only survivors without heart transplantation (HTx) or a mechanical assist device and patients who died suddenly were analyzed. All data were obtained at time of first evaluation on the same day, except for LVEF, which was measured within one month before or after entry into the study. Outcome was documented during an observation period up to three years. In case of death, the underlying cause was obtained from the hospital chart or from interviews with relatives. Deaths were classified as sudden death, pump failure, or resulting from other causes. Sudden death was defined as witnessed cardiac arrest or death within 1 hour after the onset of acute symptoms or unexpected, unwitnessed death (i.e., during sleep) in a patient known to have been well within the previous 24 hours. Deaths resulting from deterioration of CHF with progression of congestive symptoms were classified as pump failure.	A Cox proportional hazard regression analysis was performed to identify independent predictors of sudden death, including only survivors without HTx and without implantation of a mechanical left ventricular assist device and patients with sudden death. The model was built stepwise, and *P* value for entering and staying in the model was set at 0.05. Because BNP, N-BNP, and N-ANP were not normally distributed, log BNP, log N-BNP, and log ANP plasma levels were used for analysis. A log BNP cutoff point was selected to define a large patient group with low risk of sudden death. Kaplan-Meier lifetime analysis was used for survival comparison between patient groups stratified according to this cutoff point.

AF Atrial fibrillation.
AFL Atrial flutter.

AMI	Acute myocardial infaction.
ANOVA	Analysis of variance
ANP	Atrial natriuretic peptide.
BNP	B-type natriuretic peptide.
BRS	Baroreflex sensitivity.
CAD	Coronary artery disease.
CD	Cardiac death.
CHART	Chronic heart failure analysis and registry.
CHF	Congestive heart failure.
CI	Confidence interval.
DC	Direct current.
DCM	Dialated cardiomyopathy.
ECG	Electrocardiogram.
EF	Endothelial function.
EPS	Electrophysiologic study.
HRV	Heart rate variability.
HTx	Heart transplantation.
ICD	Implantable cardioverter defibrillator.
LVDD	Left ventricular diastolic diameter.
LVEF	Left ventricular ejection fraction.
LVH	Left ventricular hypertrophy.
MI	Myocardial infarction.
MUSTT	Multicenter unsustained tachycardia trial.
NYHA	New York Heart Association.
PTCA	Percutaneous transluminal coronary angioplasty.
RR	Relative risk.
QTd	QT dispersion.
SCD	Sudden cardiac death.
SPECT	Single photon emission computed tomography.
SVT/VF	Sustained ventricular tachycardia/ventricular fibrillation
TWA	T-wave alternans.
VALIENT	Valsartan in acute myocardial infarction trial.
VF	Ventricular fibrillation.
VHD	Valvular heart disease.
VT	Ventricular tachycardia.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Questions 5 and 6 are presented in Table 76. This assessment examined each study to determine if there was evidence of potential source of bias. Biases were grouped into three categories: (1) biases pertaining to design; (2) biases pertaining to data collection; and (3) biases in analysis. This assessment found that the included studies appeared to be free of many biases; the most common biases found in these studies were volunteer bias (those who agree to participate in a study may differ from those who refuse), withdrawal bias (those who withdraw from a longitudinal study may differ from those who continue), and confounding factors (i.e., factors associated with the disease). As a result, this assessment determined that the quality of the included studies was not high; rather, they were of low-to-moderate quality. It is important to note that even though some studies appeared to be free of all potential biases, they used observational study designs that are susceptible to bias by virtue of their design. Thus, even a perfectly designed and executed observational study cannot be graded as high quality.

Table 76. Quality Assessment of Studies on Risk of Sudden Death or Incapacitation in Individuals with Low LVEF

Reference	Year	Evidence of Potential Source of Bias?							
		Biases Pertaining to Design				Biases Pertaining to Data Collection			Biases in Analysis
		Membership Bias	Nonrespondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
Studies That Used Multiple Levels of LVEF Stratification									
Watanabe et al.(275)	2006	No	No	No	No	No	No	No	Yes
Solomon et al.(276)	2005	No	No	Yes	No	No	No	No	Yes
Buxton et al.(277)	2002	No	No	Yes	No	No	No	No	Yes
Adachi et al.(279)	2001	No	No	No	No	No	No	No	Yes
Sharir et al.(280)	2001	No	No	No	No	No	Yes	No	Yes
Studies That Did Not Use Multiple Levels of LVEF Stratification									
Pedersen et al.(284)	2006	No	No	No	No	No	Yes	No	Yes
Balanescu et al.(285)	2004	No	No	No	No	No	No	No	Yes
Raczak et al.(281)	2004	No	No	No	No	No	No	No	Yes

Reference	Year	Evidence of Potential Source of Bias?							
		Biases Pertaining to Design				Biases Pertaining to Data Collection			Biases in Analysis
		Membership Bias	Nonrespondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
La Rovere et al.(282)	2003	No	No	No	No	No	No	No	Yes
Berger et al.(283)	2002	No	No	Yes	No	No	No	No	Yes

Generalizability of Evidence to Target Population

None of the studies featured in this section of the cardiovascular report specifically included information about the occupations of the participants, therefore making it impossible to generalize on the basis of employment. Table 77 presents the demographics of the patients included in these studies. Patients in these studies were at least somewhat representative of the CMV driver population in that they were predominately older males (60% to 91% males, 48 to 73 years of age).

Findings

This subsection provides a brief description of the key findings regarding LVEF in the 10 studies that comprised the evidence base we used for determining the risk of sudden death or incapacitation in individuals with low LVEF. The authors' conclusions regarding LVEF and risk of sudden death or incapacitation in each of the included studies are presented in Table 77, followed by a detailed summary of the findings from each study. The 10 included studies were divided according to whether or not the study used multiple levels of LVEF stratification.

Table 77. Studies on Risk of Sudden Death or Incapacitation in Individuals with Low LVEF

Study	Year	Number of Patients	Patient Demographics	Authors' Conclusions Regarding LVEF and Risk of Sudden Death or Incapacitation	Cause of Death or Incapacitation
Studies That Used Multiple Levels of LVEF Stratification					
Watanabe et al.(275)	2006	680 patients	Age mean ±SD (median): 66 ±14 (68) Male (%): 469 (69) LVEF % (median): 42 ±14 (41)	In summary, reduced LVEF (<30%) was significantly associated with an increased risk of sudden death in patients with CHF. Rather than particular risk markers, the number of accumulated risk markers was strongly associated with an increased risk of sudden death. Patients with 3 or more risk markers showed a substantial increase in sudden death mortality compared to patients with 2 or less risk markers. Reduced LVEF was one of the risk markers, but did not have a particular power for predicting sudden death in patients with CHF.	The underlying etiology of CHF was divided into 54 categories, i.e., dilated cardiomyopathy (DCM), coronary artery disease (CAD), valvular heart disease (VHD), and left ventricular hypertrophy (LVH).
Solomon et al.(276)	2005	14,609 total patients 11,256 patients in which the LVEF was determined	**Sudden death or cardiac arrest with resuscitation (N = 1,067)** Age mean ±SD: 67.8 ±11.2 Male (%): 67 LVEF mean ±SD: 0.32 ±0.10 **Death from cause other than sudden death (N = 1,905)** Age mean ±SD: 71.4 ±10.3 Male (%): 61 LVEF mean ±SD: 0.33 ±0.10 **Survival free of sudden death or cardiac arrest with resuscitation (N = 11,637)** Age mean ±SD: 63.5 ±11.7 Male (%): 70 LVEF mean ±SD: 0.36 ±0.10	The risk of sudden death is highest soon after myocardial infarction — particularly during the first 30 days. This risk is greatest among patients with the lowest LVEF (≤30%), but even patients with a high LVEF (>40%) are at substantially increased risk in the early postinfarction period, as compared with the subsequent risk, and the discriminatory effect of the LVEF declines over time.	Not Reported
Buxton et al.(277)	2002	1,791 total patients 429 patients had inducible sustained ventricular tachyarrhythmia 1,362 patients did not have inducible randomizable tachyarrhythmias	Median LVEF: 29%	Both low LVEF and inducible tachyarrhythmias identify patients with coronary disease at increased mortality risk. LVEF does not discriminate between modes of death, whereas inducible tachyarrhythmia identifies patients for whom death, if it occurs, is significantly more likely to be arrhythmic, especially if LVEF is ≥30%.	Arrhythmic death or cardiac arrest

Study	Year	Number of Patients	Patient Demographics	Authors' Conclusions Regarding LVEF and Risk of Sudden Death or Incapacitation	Cause of Death or Incapacitation
Adachi et al.(279)	2001	64 patients	**Arrhythmic events group (n = 10)** Age mean ±SD: 55 ±12 years Male: 9 (90%) Female: 1 (10%) LVEF (%): 34 ±13 **Nonevent group (n = 54)** Age mean ±SD: 48 ±14 years Male: 43 (80%) Female: 11 (20%) LVEF mean ±SD (%): 47 ±13	T-wave alterans (TWA) for the electrical substrate and the LVEF for the hemodynamic function are useful risk stratifiers for patients with DCM. This study suggests that analysis of TWA and determination of the LVEF are useful screening tests for determining the indication for ICD therapy, and thus lessening the risk of sudden cardiac death, in patients with DCM.	Not Reported
Sharir et al.(280)	2001	2,686 patients	Age mean ±SD: 66 ±12 years Male: 1,636 (60.9%) LVEF mean ±SD: 58 ±5 Cardiac death: 57 (2.12%) Nonfatal myocardial infarction: 30 (1.12%)	After adjustment for prescan information, the amount of ischemia was the best predictor of nonfatal myocardial infarction, and the poststress LVEF was the best predictor of cardiac death. The amount of ischemia and the left ventricular functional status ought to be integrated to improve stratification of patients into low, intermediate, and high risk of CD and can assist in determining the appropriate treatment strategy for the individual patient.	Cardiac death or myocardial infarction
Studies That Did Not Use Multiple Levels of LVEF Stratification					
Pedersen et al.(284)	2006	5,983 total patients 1,149 patients with sustained or paroxysmal AF/AFL 4,834 patients without sustained or paroxysmal AF/AFL	**With AF/AFL** median age: 73 years 65% male median LVEF: 0.39 **No AF/AFL** median age: 66 years 70% male median LVEF: 0.45	Total mortality, sudden cardiac death, and nonsudden cardiac death were increased by low LVEF.	Not Reported

Study	Year	Number of Patients	Patient Demographics	Authors' Conclusions Regarding LVEF and Risk of Sudden Death or Incapacitation	Cause of Death or Incapacitation
Balanescu et al.(285)	2004	463 total patients 211 were treated by thrombolysis or primary PTCA 252 patients received conventional therapy	**All patients** Age mean ±SD: 60.6 ±13 years 312 males, 151 females **Reperfusion therapy patients** Age mean ±SD: 60.3 ±13.6 years Males: 150 (71.1%) LVEF mean ±SD: 43.8 ±7.9 Total mortality: 19 (9%) Sudden death: 5 (2.4%) **Conventional treatment patients** Age mean ±SD: 60.9 ±12.6 years Males: 162 (64.3%) LVEF mean ±SD: 37.1 ±8.3 Total mortality: 49 (19.4%) Sudden death: 17 (6.7%)	Heart rate variability parameters have prognostic value independent from LVEF and spontaneous ventricular arrhythmias one year after acute myocardial infarction.	Not Reported
Raczak et al.(281)	2004	112 total patients 56 patients experienced ICD discharge for fast VT or VF or sudden death (event + group) 56 patients did not experienced ICD discharge for fast VT or VF or sudden death (event - group)	**All patients** Age mean ±SD: 61 ±10 years M/F: 90/22 LVEF mean ±SD: 37 ±12 **Event + group** Age mean ±SD: 60 ±10 years M/F: 44/12 LVEF mean ±SD: 34 ±10 **Event - group** Age mean ±SD: 62 ±9 years M/F: 46/10 LVEF mean ±SD: 39 ±13	Baroreflex sensitivity (BRS) was a powerful univariate predictor of sudden death. There was a strong interaction between BRS and LVEF. BRS was a particularly useful predictor in those with an impaired LVEF.	Arrhythmic death
La Rovere et al.(282)	2003	202 patients	Age median (interquartile range) : 54 (13) years Male, %: 87 LVEF median (interquartile range): 23 (8)	There was a significant association between LVEF ≤21% and arrhythmic mortality.	Arrhythmic death

Study	Year	Number of Patients	Patient Demographics	Authors' Conclusions Regarding LVEF and Risk of Sudden Death or Incapacitation	Cause of Death or Incapacitation
Berger et al.(283)	2002	452 total patients	**All patients (n = 452)** Age mean ±SD: 54 ±10 years Male: 395 (87%) Female: 57 (13%) LVEF mean ±SD: 20 ±7 **Patients with sudden death (n = 44)** Age mean ±SD: 55 ±10 years Male: 40 (91%) Female: 4 (9%) LVEF mean ±SD: 17 ±7 **Patients with pump failure (n = 31)** Age mean ±SD: 61 ±7 years Male: 28 (90%) Female: 3 (10%) LVEF mean ±SD: 17 ±6 **Surviving patients (n = 293)** Age mean ±SD: 53 ±11 years Male: 253 (86%) Female: 40 (14%) LVEF mean ±SD: 21 ±7	There was a significant association between LVEF and sudden death.	Not Reported

AF/AFL Atrial fibrillation/atrial flutter.
BRS Baroreflex sensitivity.
CAD Coronary artery disease.
CD Cardiac death.
CHF Congestive heart failure.
DCM Dialated cardiomyopathy.
ICD Implantable cardioverter defibrillator.
LVEF Left ventricular ejection fraction.
LVH Left ventricular hypertrophy.
PTCA Percutaneous transluminal coronary angioplasty.
SD Standard deviation.
TWA T-wave alternans.
VF Ventricular fibrillation.
VHD Valvular heart disease.
VT Ventricular tachycardia.

Studies that Stratified by LVEF

Five studies reported the risk of sudden death or incapacitation in individuals with low LVEF using multiple levels of LVEF stratification. The five studies are extremely heterogeneous with each examining the relationship between LVEF and sudden death or incapacitation from different perspectives. Consequently, we determined that the best way to communicate the findings of these studies was to present the findings of each study separately. The findings from each of the five studies included in this section of the evidence report are presented below.

In **Watanabe et al.,(275)** the authors reported the following regarding LVEF:

- Sudden death was increased by LVEF <30% with a hazard ratio of 2.31 (95% CI: 1.14 – 4.68).
- There was no difference in the probability of sudden death between patients with LVEF <30% and 0 to 1 other risk markers and those with LVEF ≥30% and 0 to 2 other risk markers (the total number of risk markers <3) (Figure 25). Furthermore, there was no difference in the probability of sudden death between patients with LVEF <30% and 2 to 4 other risk markers and those with EF ≥30% and 3 to 4 other risk markers (the total number of risk markers ≥3).

Figure 25. Kaplan–Meier Analysis for Sudden Death in Patients who were Grouped by a Combination of Low EF and the Number of Other Risk Markers

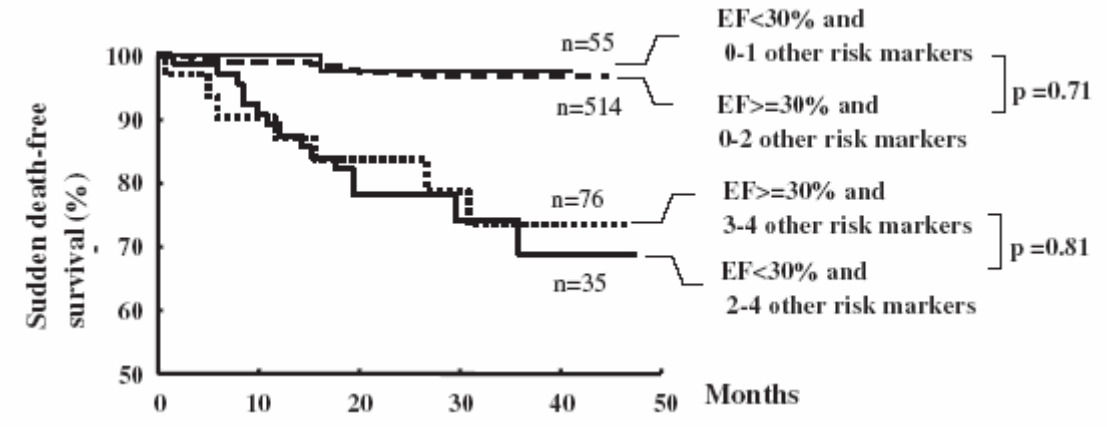


Figure from Watanabe et al.(275)
Note: The incidence of sudden death was dependent on the total number of the risk markers including low EF.

- The predictive performance of LVEF <30% for sudden death was as follows: sensitivity = 0.44, specificity = 0.82, positive predictive value = 0.12, and negative predictive value = 0.96.

In Solomon et al. 2005(276), the authors reported the following regarding LVEF:

- The increased early incidence of sudden death or cardiac arrest with resuscitation was most apparent among patients with an LVEF ≤30%: the incidence rate during the first 30 days was 2.3% per month (95% CI, 1.8 to 2.8%) (Figure 26 and Figure 27).

Figure 26. Kaplan-Meier Estimates of the Rates of Sudden Death or Cardiac Arrest with Resuscitation, According to the LVEF

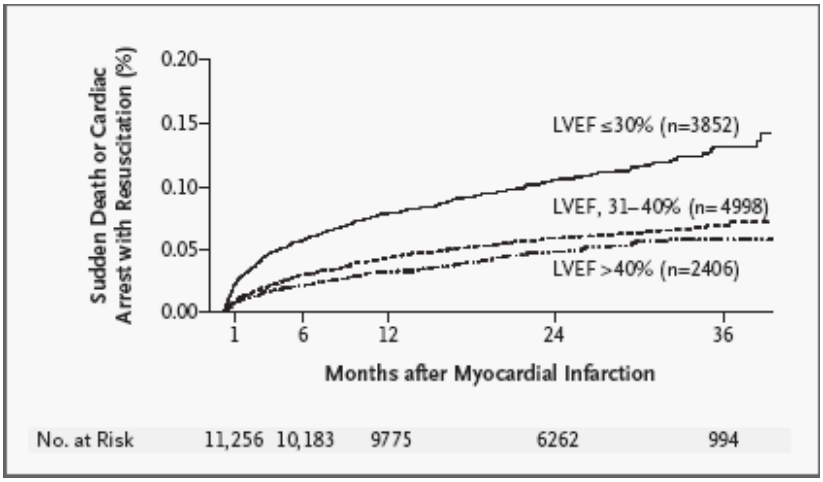


Figure from Solomon et al.(276)

Figure 27. Rates of Sudden Death or Cardiac Arrest with Resuscitation Over the Course of the Trial in the Three Categories of LVEF

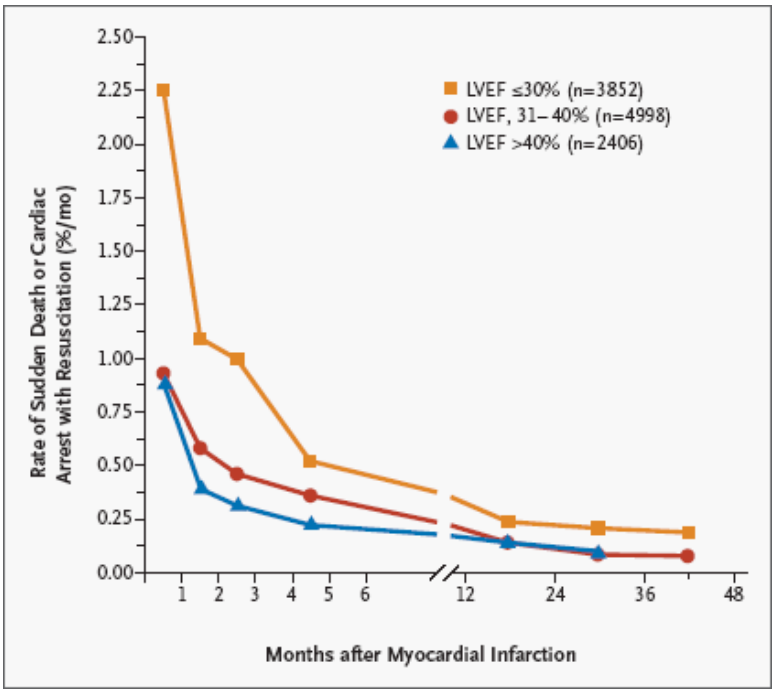


Figure from Solomon et al.(276)

- Of the 156 sudden deaths or episodes of cardiac arrest with resuscitation that occurred during the first 30 days, 85 occurred among the 3,852 patients with an LVEF ≤30% (54%; 1% of all patients with a known LVEF).
- Of the 3,852 patients with an LVEF ≤30%, 399 (10%) died suddenly or had cardiac arrest with resuscitation during the trial, as compared with 295 of the 4,998 patients with an LVEF of 31 to 40% (6%) and 119 of the 2,406 patients with an LVEF >40% (5%).
- Among the patients with a known LVEF, 49% of all sudden deaths or cardiac arrests with resuscitation occurred in patients with an LVEF ≤30%. This proportion remained relatively constant throughout follow-up.
- Among the 399 patients with an LVEF ≤30% who died suddenly or had cardiac arrest with resuscitation, 85 (21%) did so during the first 30 days after MI, as compared with 50 of 295 such patients with an LVEF of 31% to 40% (17%) and 21 of 119 such patients with an LVEF >40% (18%).

- Among patients with an LVEF >40%, the rate of sudden death or cardiac arrest with resuscitation was more than six times as high in the first month as after one year.
- Although the incidence of sudden death or cardiac arrest with resuscitation declined markedly over time in all groups, the relative risk of these events remained two to three times as high as among patients with an LVEF ≤30% as among patients with an LVEF >40%. However, overall, the absolute rate after two years was substantially lower than during the early period.
- When the LVEF was considered as a continuous variable, each decrease of 5 percentage points in the LVEF was associated with a 21% increase in the risk of sudden death or cardiac arrest with resuscitation during the first 30 days after MI (hazard ratio, 1.21; 95% CI, 1.10 to 1.30), after adjustment for all known baseline covariates.

In **Buxton et al.,(277)** the authors reported the following regarding LVEF:

- The 5-year mortality rate of all patients with EF <30% (54%) was significantly higher than that of patients having an EF ≥30% (36%, *P* = 0.0001). This difference occurred in patients with and without inducible tachyarrhythmia (Table 78). Over the course of five years, the mortality curves of patients based on inducibility and EF remained distinct (Figure 28); that is, both EF and inducibility contributed to mortality risk.

Table 78. Relation Between Inducible Tachyarrhythmia, EF, and Kaplan-Meier Event Rates among Untreated Patients in MUSTT

	Inducible			Noninducible		
	EF <30% (n=217)	EF ≥30% (n=212)	*P*	EF <30% (n=690)	EF ≥30% (n=672)	*P*
2-Year mortality	0.33	0.22	0.0046	0.26	0.15	0.0001
5-Year mortality	0.57	0.43		0.54	0.34	
2-Year AD/CA	0.21	0.16	0.0845	0.15	0.08	0.0001
5-Year AD/CA	0.40	0.30		0.31	0.17	

Inducible/noninducible indicates presence/absence of inducible sustained randomizable ventricular tachyarrhythmia at baseline electrophysiological study; EF, ejection fraction; mortality, total mortality rates; and AD/CA, rate of arrhythmic death and cardiac arrest.

P values refer to Cox model comparison of overall mortality and of AD/CA in patients with EF <30% vs ≥30%, respectively.

Table from Buxton et al. 2002(277)

Figure 28. Relation between EF, Inducible VT, and Total Mortality Rate

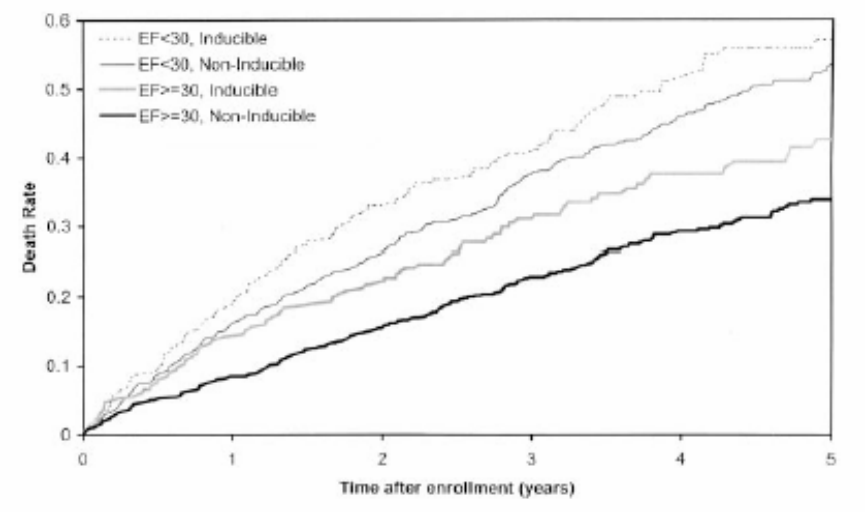


Figure from Buxton et al. 2002(277)

- The 5-year risk of arrhythmic death or cardiac arrest of all patients with EF <30% (33%) was significantly higher than that of patients having an EF ≥30% (20%, *P* = 0.0001). The increased risk of arrhythmic death or cardiac arrest with a low EF was present in patients without inducible tachyarrhythmia (*P* = 0.0001), and a similar trend was observed for patients with inducible tachyarrhythmia (Table 78). As noted for total mortality over the course of five years, the arrhythmic death/cardiac arrest event curves based on inducibility and EF remained distinct (Figure 29).

Figure 29. Relation between EF, Inducible VT, and Rate of Arrhythmic Death or Cardiac Arrest

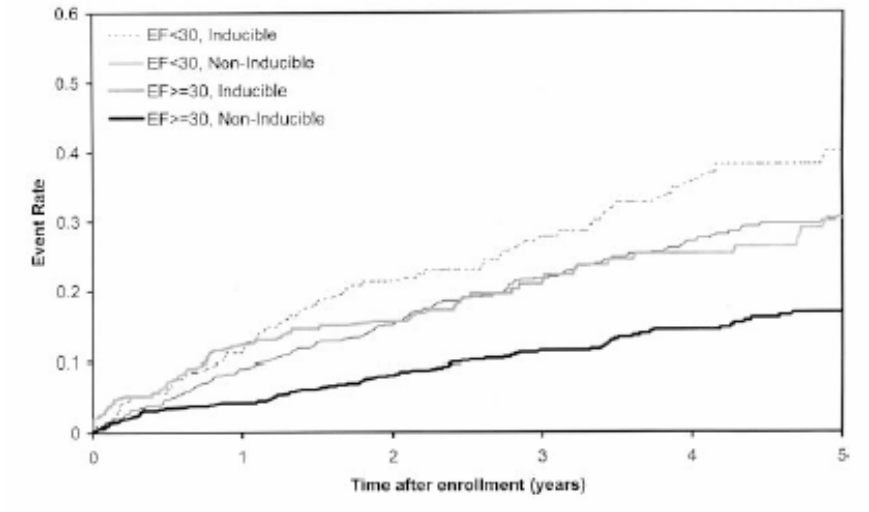


Figure from Buxton et al. 2002(277)

- Multivariable analysis confirmed that both EF and inducible VT were independent predictors of total mortality and arrhythmic death/cardiac arrest (Table 79). Although inducibility is a modest predictor of total mortality (hazard ratio 1.22, *P* = 0.0202), it has a stronger relationship with arrhythmic death/cardiac arrest (hazard ratio 1.62, *P* = 0.0001).

Table 79. Adjusted Cox Models*

	Total Mortality			Arrhythmic Death or Cardiac Arrest		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
EF (5% decrease from EF 40% to 20%)	1.18	1.12, 1.25	0.0001	1.19	1.10, 1.29	0.0001
EF <30%	1.53	1.31, 1.78	0.0001	1.53	1.23, 1.89	0.0001
Inducibility	1.22	1.03, 1.44	0.0202	1.63	1.31, 2.02	0.0001

EF indicates ejection fraction.

*Adjusted for age, sex, race, duration (in beats) of longest episode of nonsustained ventricular tachycardia, number of vessels with 75% or greater stenosis, left bundle-branch block, intraventricular conduction delay, use of digitalis at baseline, previous myocardial infarction, prior bypass surgery, prior angioplasty, and symptoms of angina within 6 weeks before enrollment.

Hazard ratios for each end point are depicted, with ejection fraction treated as a continuous variable (EF, 5% decrease from EF 40% to 20%) and dichotomized around the median value (<30%).

Table from Buxton et al.(277)

- The relation between EF and event rates was highly significant whether EF was treated as a continuous or dichotomized variable (Table 79). When EF was treated as a continuous variable, the rates of both total mortality and

arrhythmic death or cardiac arrest decreased monotonically as ejection fraction increased from 25% to 40% (Figure 30). In addition, the hazard ratios for both mortality and arrhythmic death/cardiac arrest as related to EF were nearly identical. This supports the conclusion that EF is not effective in discriminating mode of death. In contrast, the hazard ratio for arrhythmic death/cardiac arrest was greater than that for total mortality when related to the presence of inducible VT. Thus, inducible VT is a relatively specific predictor of arrhythmic deaths.

Figure 30. Relation of EF and Total Mortality or Arrhythmic Death/Cardiac Arrest, with EF Treated as a Continuous Variable

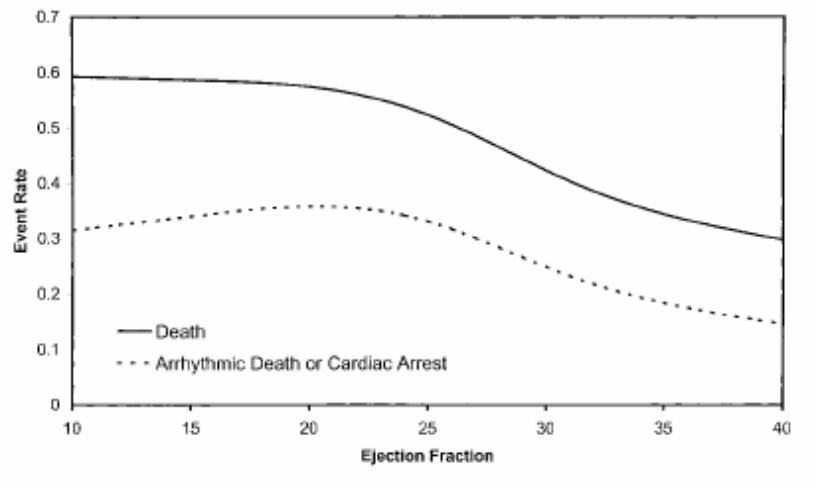


Figure from Buxton et al.(277)

In **Adachi et al.,(279)** the authors reported the following regarding LVEF:

- The LVEF in the arrhythmic events group was 34±13% and 47±13% in the nonevent group (p <0.01).
- The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LVEF for arrhythmic events are shown in Table 80.

Table 80. TWA and Conventional Risk Markers as Predictors for Event-free Survival

	Se (%)	Sp (%)	PPV (%)	NPV (%)	RR	p value (χ² test)
TWA	90	61	30	97	10.2	0.0029
LVDd	30	85	27	87	2.06	0.2423
LVEF	70	80	39	93	5.96	0.0013
NSVT	80	67	31	95	5.85	0.0053
SAECG	40	80	27	88	2.18	0.1783
QTd	40	91	44	89	4.07	0.0102

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; TWA, T-wave alternans; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion.

Table from Adachi et al.(279)

- Kaplan-Meier actual survival analysis was used to ascertain the ability of LVEF to predict event-free survival. Univariate Kaplan-Meier survival analysis revealed that LVEF (Figure 31) was statistically significant according to the log-rank test ($p < 0.005$). The significant factors detected by univariate analysis were then assessed by multivariate analysis. Using the Cox proportional hazard model, LVEF were found to be statistically significant predictors of 37 months of event-free survival ($p < 0.01$).

Figure 31. Kaplan-Meier Survival Curves of Patients with LVEF ≤35% / LVEF >35%

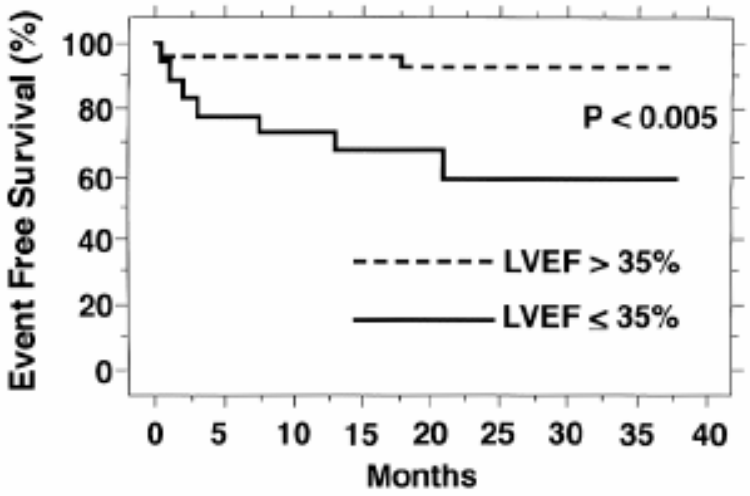


Figure from Adachi et al. 2001(279)

- To evaluate risk stratification with a 2-variable model, the authors used the combination of the LVEF for the hemodynamic function with the T-wave alternan (TWA), nonsustained ventricular tachycardia (NSVT), signal-

averaged electrocardiography (SAECG), and QT dispersion (QTd) for the electrical substrate. Kaplan-Meier survival analysis was used to ascertain the ability of 4 sets of 2-variable risk stratifiers (LVEF ≤35% with TWA+, LVEF ≤35% with NSVT+, LVEF ≤35% with SAECG+, and LVEF ≤35% with QTd >90 ms). The sensitivity, specificity, PPV, and NPV of the 2-variable models for arrhythmic event are shown in Table 81. Univariate Kaplan-Meier survival analysis revealed that the combinations of an LVEF ≤35% with TWA+ (Figure 32), LVEF ≤35% with NSVT+, and LVEF ≤35% with a QTd >90 ms were statistically significant according to the log-rank test ($p < 0.005$, $p < 0.05$, and $p < 0.05$, respectively). The significant factors detected by univariate analysis were reassessed by multivariate analysis. Multivariate Cox regression analysis revealed that the combination of an LVEF ≤35% with TWA+ was the only statistically significant independent risk factor ($p < 0.01$). None of the 30 patients with TWA and an LVEF >35% experienced an arrhythmic event ($p < 0.05$); that is, the very low-risk patients with DCM.

Table 81. Prediction of Event-free Survival with Two Variable Models

	Se (%)	*Sp (%)*	*PPV (%)*	*NPV (%)*	*RR*	*p value (* test)*
LVEF≤35% NSVT(+)	*50*	*85*	*38*	*90*	*3.92*	*0.0111*
LVEF≤35% SAECG(+)	*20*	*94*	*40*	*86*	*2.95*	*0.1180*
LVEF≤35% QTd>90 ms	*20*	*96*	*50*	*87*	*3.75*	*0.0405*
LVEF≤35% TWA(+)	*60*	*85*	*43*	*92*	*5.36*	*0.0015*

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion; TWA, T-wave alternans.

Table from Adachi et al. 2001(279)

Figure 32. Kaplan-Meier Survival Curves of Patients with LVEF ≤35%, Positive TWA / Not LVEF ≤35%, Positive TWA

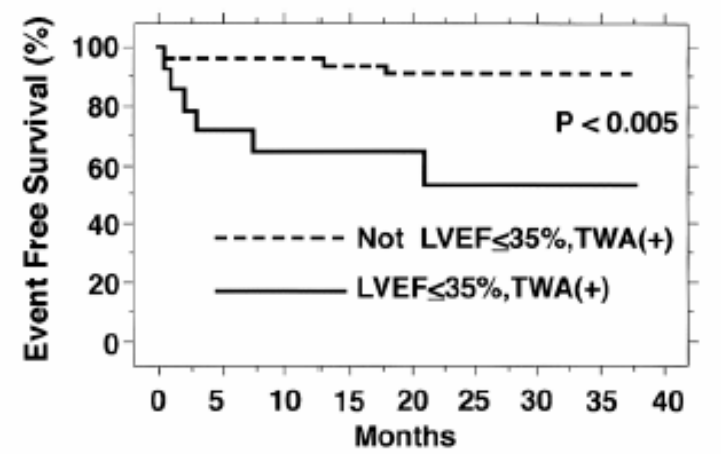


Figure from Adachi et al. 2001(279)

In **Sharir et al.,(280)** the authors reported the following regarding LVEF:

- Univariate Cox proportional hazards regression analysis of prescan, perfusion, and function data showed that the best predictor of cardiac death (CD) was the LVEF (χ^2, 84.3; *P* <0.0001). Prediction of MI by LVEF, although significant, was substantially weaker (χ^2, 8.7; *P* = 0.003) than by sudden death syndrome.

- Figure 33 shows an inverse relationship between the average CD rate (%/y) and the LVEF. Values of the LVEF were obtained by averaging over 10% intervals. This relationship was best fitted by an exponential curve, yielding a high correlation coefficient ($y = 28.5 \times e^{-0.063x}$; *r* = -0.99, *P* <0.005). According to this curve estimate, the CD rate exceeded 1%/y for LVEF ≤50% and 4%/y for LVEF <30%. On the basis of this equation, the study group was stratified into the following three risk categories of CD: (a) LVEF >50%, low risk (CD rate, <1%/y); (b) LVEF 30% to 50%, intermediate risk (CD rate, 1% to 4%/y); and (c) LVEF <30%, high risk (CD rate >4%/y). Kaplan–Meier survival analysis showed a decrease in survival with decreasing LVEF (*P* <0.000001) (Figure 34). The large gap between survival curves of patients with an LVEF between 30% and 50% and patients with an LVEF <30% is attributed to the exponential relationship between cardiac mortality and the LVEF.

Figure 33. Annual CD Rate as Function of LVEF

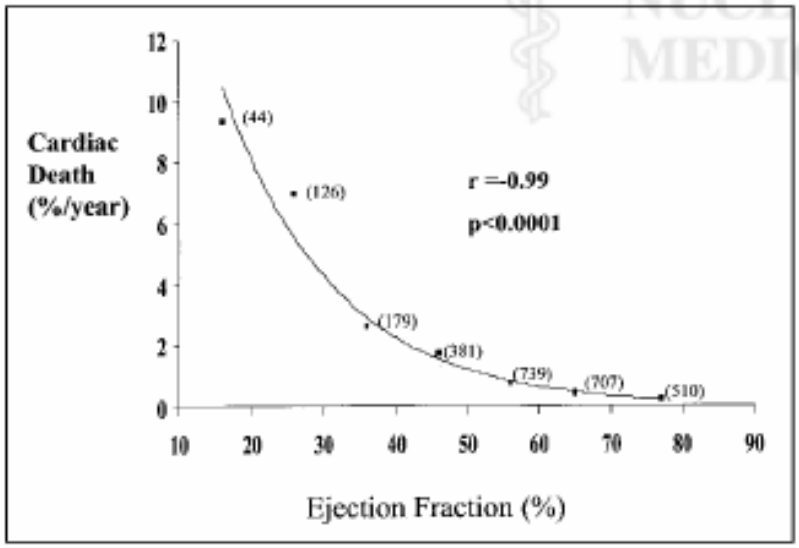


Figure from Sharir et al. 2001(280)
Note: Number of patients at each 10% interval is indicated in parentheses.

Figure 34. Cumulative Survival with Stratification by LVEF

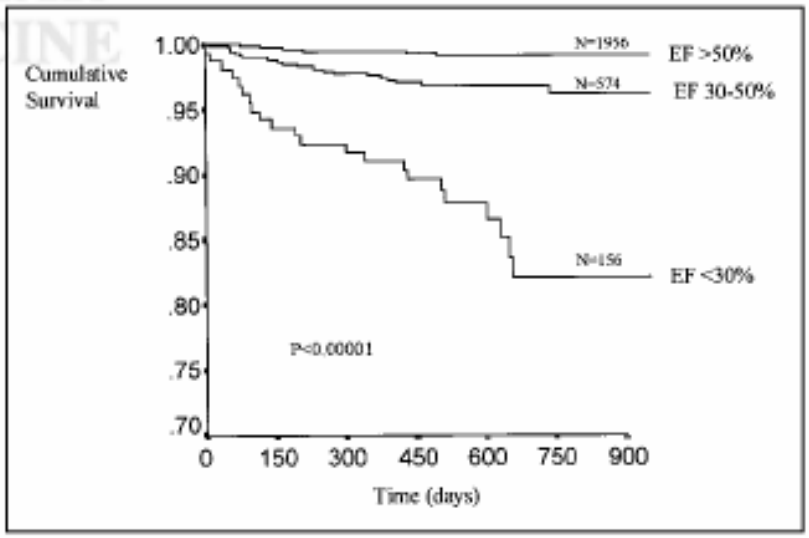


Figure from Sharir et al. 2001(280)
Note: Number of patients in each subgroup is indicated.

Studies that Did Not Use Multiple Levels of LVEF Stratification

Five studies reported the risk of sudden death or incapacitation in individuals with low LVEF without stratifying by LVEF. As was the case above, the five studies are extremely heterogeneous with each examining the relationship between LVEF and sudden death or incapacitation from different perspectives. Consequently, we determined that the best way to communicate the findings of these studies was to present the findings of each study separately. The findings from each of the five studies included in this section of the evidence report are presented below.

In **Pedersen et al.,(284)** the authors reported the following regarding LVEF:

- Total mortality was increased by low LVEF with a risk ratio of 1.57 (95% CI: 1.41-1.75; p <0.0001).
- SCD was increased by low LVEF with a risk ratio of 1.73 (95% CI: 1.42-2.09; p <0.0001).
- Nonsudden CD was increased by low LVEF with a risk ratio of 1.41 (95% CI: 1.19-1.65; p <0.0001).

In **Balanescu et al.,(285)** the authors reported the following regarding LVEF:

- The twelve parameters correlating with mortality in unvaried analysis were entered in a Cox proportional hazard regression model to assess independent predictors of survival at one year after myocardial infarction (age, standard deviation of normal-to-normal intervals (SDNN) <50 ms, root mean square successive difference (rMSSD) <20 ms[32], HF power <700 ms^2, LF power >1,500 ms^2, LF/HF ratio >2[33], total spectral power <2,500 ms^2, LVEF <40%; ventricular couplets, nonsustained VT, silent ST segment depression >1 mm, and more than 5 silent ischemic episodes per 24 hours). Independent predictors of total mortality 1 year after AMI were LVEF <40%, bursts of nonsustained VT, and three heart rate variability (HRV) parameters: low SDNN and rMSSD and LF/HF

[32] SDNN and rMSSD represent time-domain parameters of heart rate variability.

[33] LF and HF represent frequency-domain parameters of heart rate variability.

ratio >2 (Table 82). The relative risks of the calculated HRV parameters, LVEF, spontaneous ventricular arrhythmias, and the presence of silent ischemia for total mortality are displayed in Figure 35.

Table 82. Independent Predictors of Total Mortality According to Cox Multivariate Regression Analysis

	DF	Coef	Std. error	Coef/SE	Chi-square	P-to-remove	Exp (Coef)
SDNN <50:T	1	0.763	0.276	2.762	7.630	0.0057	2.144
rMSSD <20:T	1	2.067	0.406	5.098	25.994	<0.0001	7.905
LF/HF >2:T	1	1.380	0.363	3.803	14.463	0.0001	3.974
NSVT mom 21:T	1	0.65	0.259	2.507	6.284	0.0122	1.915
LVEF <40:T	1	0.982	0.489	2.011	4.042	0.0444	2.671

Model coefficients for: 365 days FU; Censor variable: 1 year death; Model: Cox proportional hazards; Step: 5

Table from Balanescu et al. 2004(285)

Figure 35. Relative Risks for Death of HRV Parameters, LVEF, Spontaneous Ventricular Arrhythmias, and Silent Myocardial Ischemia, Which in Univariate Analysis were Correlated with 1-year Total Mortality

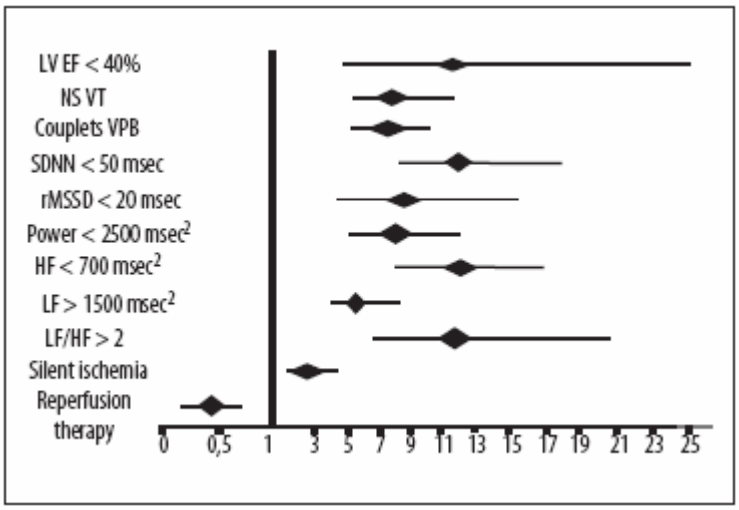


Figure from Balanescu et al. 2004(285)

Note: Horizontal bars indicate 95% CI.

In **Raczak et al.,(281)** the authors reported the following regarding LVEF:

- LVEF was significantly lower among the event+ patients compared to the event- patients (34 ±10% vs 39 ±13%, p = 0.022).
- Table 83 reports the univariate predictors of an arrhythmic event. A depressed baroreflex sensitivity (BRS) (≤3.3 ms/mmHg) showed the strongest

association with the occurrence of an event with an RR of 2.3 (95% CI 1.3–4.0), followed by LVEF ≤35% with an RR of 2.0 (95% CI 1.2-3.6).

Table 83. Significant Univariate Predictors of an Event

Variables (cut-off value)	• ²	*p value*	*RR*	*95%CI*
LVEF ≤35%	*6.1*	*0.013*	*2.0*	*1.2–3.6*
NYHA >2	*4.4*	*0.036*	*1.8*	*1.1–3.0*
BRS ≤3.3 ms/mmHg	*8.4*	*0.004*	*2.3*	*1.3–4.0*

Table from Raczak et al. 2004(281)

In **La Rovere et al.,(282)** the authors reported the following regarding LVEF:

- Univariate Cox regression analysis found a significant association between LVEF ≤21% and arrhythmic mortality (χ^2, 4.2; *P* = 0.04), with a relative risk of 2.6 (95% CI 1.1-6.5).

In **Berger et al.,(283)** the authors reported the following regarding LVEF:

- Univariate Cox proportional hazards model analysis found a significant association between LVEF and sudden death (χ^2, 7.7377; *P* = 0.0054)

Section Summary

Decreasing LVEF increases the risk for sudden death or incapacitation among individuals with CVD (Strength of Evidence: Moderate)

- **Due to the fact that no more than two studies used the same levels of LVEF stratification, no attempt was made to determine a quantitative estimate of the risk of sudden death or incapacitation in individuals with low LVEF.**

  Ten low-to-moderate quality studies assessed the risk of sudden death or incapacitation in individuals with low LVEF. Five of these studies(275-277,279,280) used multiple levels of LVEF stratification. The remaining five studies(281-285) used a single level of LVEF stratification. These 10 studies consistently demonstrated that decreasing LVEF increases the risk of sudden death or incapacitation in individuals with CVD. However, several studies have indicated that although LVEF is an important risk factor for sudden death or incapacitation, it is not the only risk factor. In order to better predict sudden death or incapacitation, one should include other risk factors with

LVEF.(275,277,279-281,284,285) For example, Watanabe et al.(275) noted that rather than using particular risk markers, the use of a number of accumulated risk markers was a more powerful predictor for sudden death in patients with chronic heart failure.

Key Question 6: Is the relationship between LVEF and sudden death or incapacitation (if established) dependent on the underlying etiology of heart failure?

Background

Our previous analysis found that LVEF is an important predictor of sudden death and incapacitation. In this section we next attempt to determine whether the relationship between LVEF and sudden death or incapacitation is dependent on the underlying etiology of heart failure.

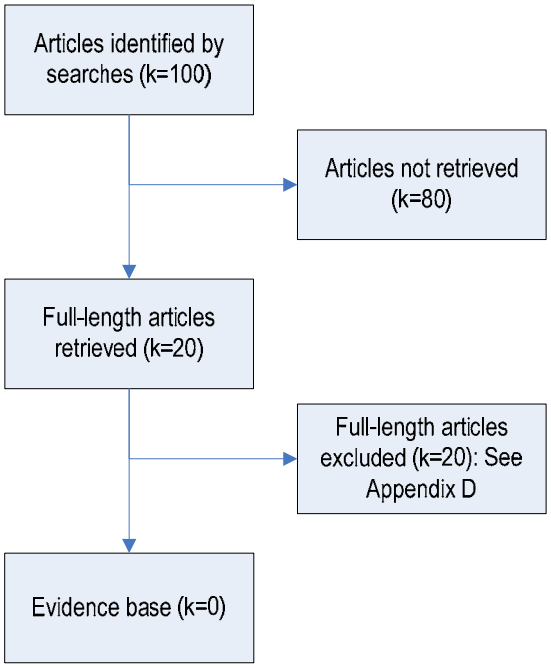
Identification of Evidence Base

The identification of the evidence used in this section of the evidence report is presented in Figure 36. Our searches[34] identified a total of 100 articles that appeared relevant. Following application of the retrieval criteria for this question, 20 full-length articles were retrieved and read in full. None of these 20 retrieved articles were found to meet our criteria for inclusion[35]. Appendix D lists the 20 articles that were retrieved but then excluded and provides the reason for their exclusion.

[34] See Appendix A for search strategies.

[35] See Appendix C for inclusion criteria.

Figure 36. Development of Evidence Base for Key Question 6



Evidence Base

No studies met the inclusion criteria for this key question.

Findings

No studies met the inclusion criteria for this key question.

Section Summary

Due to a paucity of data, no conclusion pertaining to whether the relationship between sudden death or incapacitation and LVEF is drawn.

No studies met the inclusion criteria for this key question.

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Appendix A: Search Summary

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

$	=	truncation character (wildcard) in OVID syntax
exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de.	=	limit controlled vocabulary heading in OVID syntax
.fc.	=	form/content type (PsycINFO – OVID syntax)
.fs.	=	floating subheading in OVID syntax
.hw.	=	limit to heading word in OVID syntax
.mp.	=	combined search fields in OVID syntax (default if no fields are specified)
.pt.	=	publication type in OVID syntax
.ti.	=	limit to title in OVID syntax
.tw.	=	limit to title and abstract fields in OVID syntax

EMBASE/Medline/PsycINFO

English language, human

Set Number	Concept	Search Statement
1	Sudden death	*death, sudden, cardiac/ or *death, sudden/ or *sudden death/ or sudden death.ti.
2	LVEF	Ventricular ejection fraction or *stroke volume/ or *heart ejection fraction/ or *heart left ventricle ejection fraction/
3	Risk	Exp risk/ or risk$.ti. or proportional hazard models.de. or proportional hazards model.de.
4	Combine sets	And/1-3
5	Relevant trials	(MADIT or multicenter automatic defibrillator implantation trial or MUSTT or multicenter unsustained tachycardia trial or AVID.ti. or antiarrhythmia versus implantable defibrillator trial or CASH.ti. or cardiac arrest study hamburg)
6	Implantable heart devices	(Defibrillat$.ti. or AICD.ti. or ICD$.ti. or *defibrillator/ or *defibrillators, implantable/)
7	Combine sets	1 and (5 or 6)
8	Aortic aneurysm	(Exp aortic aneurysm/ or exp aorta aneurysm/ or (aneurysm, dissecting.de. and aort$) or AAD.ti.)
9		aortic adj2 ruptur$
10	Combine sets	3 and (8 or 9)
11	Syncope	Exp syncope/ or syncop$.ti.
12	Recurrence	((recurrent disease or recurrence).de. or recur$)
13	Combine sets	And/3,11-12
14	Combine sets	Or/4,7,10,13
15	Remove overlap	Remove duplicates from 14
16	Limit by publication type	15 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
17	Limit by study type	16 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

Appendix B: Retrieval Criteria

Appendix B lists the retrieval criteria for each of the six key questions addressed in this evidence report.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with diabetes.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have CVD.

Retrieval Criteria for Key Question 2

- Articles are written in the English language.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Systematic reviews of risk factors for abdominal and TAA rupture published between January 1st, 2000, and December 1, 2006, were retrieved.
- Only studies with at least 10 patients in each treatment were retrieved.
- Only studies published after 1975 were retrieved.

Retrieval Criteria for Key Question 3

- Articles are written in the English language.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.

- Only studies with at least 10 patients in each treatment were retrieved.
- Article must describe an RCT that compared effectiveness of safety of a dual-chamber pacemaker against standard or no treatment in individuals with vasovagal syncope.

Retrieval Criteria for Key Question 4

- Articles are written in the English language.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Only studies with at least 10 patients in each treatment were retrieved.
- Article must describe a study that assessed the occurrence of crash, SCD, sudden incapacitation due to syncope, or ICD discharge during driving.

Retrieval Criteria for Key Question 5

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must have been published between January 1, 2001 and December 1, 2006.
- Article must describe a study that attempted to examine the association between risk for sudden death or incapacitation and LVEF.

Retrieval Criteria for Key Question 6

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must have been published between January 1, 2001 and December 1, 2006.
- Article must describe a study that attempted to examine the association between risk for sudden death or incapacitation and LVEF.

Appendix C: Inclusion Criteria

Appendix C will list the inclusion criteria for each of the six key questions addressed in this evidence report.

Inclusion Criteria for Key Question 1

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18 years.
- Article must describe a study that attempted to directly determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with CVD.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have CVD.
- Article must present motor vehicle crash-risk data in a manner that will allow ECRI to calculate (directly or through imputation) effect-size estimates and confidence intervals.

Inclusion Criteria for Key Question 2

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18 years.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.

- Systematic reviews of risk factors for abdominal and TAA rupture published between January 1, 2000 and December 1, 2006, are included.
- Article must score 5.0 or greater on the Newcastle-Ottawa Scale.
- Studies must have been published after during the period January 1, 1975 to the present.

Inclusion Criteria for Key Question 3

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Article must describe an RCT that compared effectiveness of safety of a dual-chamber pacemaker against standard or no treatment in individuals with vasovagal syncope.

Inclusion Criteria for Key Question 4

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18 years.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Article must describe a study that assessed the occurrence of crash, SCD, sudden incapacitation due to syncope, or ICD discharge during driving.

Inclusion Criteria for Key Question 5

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18 years.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Article must have been published between January 1, 2001 and December 1, 2006.
- Article must describe a study that attempted to examine the association between risk for sudden death or incapacitation and LVEF.

Inclusion Criteria for Key Question 6

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18 years.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Article must have been published between January 1, 2001 and December 1, 2006.
- Article must describe a study that attempted to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure.

Appendix D: Excluded Articles

Table D-1. Excluded Studies (Key Question 1)

Reference	Year	Reason for Exclusion
Antecol et al.(67)	1990	Does not provide data on crash risk
Baker(286)	1970	Does not provide data on crash risk
Bowen(287)	1973	Study did not provide data on crash risk for heart disease
Charlton et al.(75)	2004	Review
Christian(69)	1988	Does not provide data for calculating crash risk
Dischinger et al.(288)	1993	Abstract
Elgarov(289)	1993	Abstract
Furukawa(290)	1989	Risk for recurrence of MI, but does not address question of crash risk
Grattan and Jeffcoate(291)	1968	No data for calculating crash risks
Halinen(292)	1994	No data for calculating crash risks
Herner and Ysander(293)	1970	Less than 10 subjects in CVD groups
Herner et al.(71)	1966	No data for calculating crash risks
Hossack(294)	1980	Abstract
Hossack(295)	1974	No data for crash risk for CVD
Kerwin(72)	1984	No data for calculating crash risk
Myerburg(296)	1964	No data for calculating crash risk
Osawa et al.(297)	1988	Case studies
Ostrom and Eriksson(70)	1987	No data for calculating crash risk
Petch(244)	1998	Review
Petch(298)	2002	Review

Reference	Year	Reason for Exclusion
Peterson and Petty(299)	1962	No data for crash risk
Potvin et al.(300)	1993	Review
Sagberg et al.(301)	2006	Method (induced-exposure method) does not allow one to determine crash risk due to CVD when compared to non-CVD population. All individuals included in study were involved in a crash. OR for crash based on data from 67 individuals with MI at fault for a crash and 31 individuals with MI involved in a crash but not at fault.
Salzberg *et al.(302)*	1998	Study designed to evaluate the effectiveness of Washington State Department of Licensing Special Examination program. CVD data only available for 47 older individuals who passed the SEP exam. This in combination with the fact that individuals were referred to the program (presumably because of bad driving behavior) and the very high crash and violation rates observed in this population indicates that the individuals included in this study are not representative of the general or CMV driver population at large.
Schmidt(68)	1990	No data for crash risk
Sheth et al.(303)	2004	Not relevant to CVD
Simpson et al.(243)	2004	Review including Canadian driving guidelines
Sjogren et al.(304)	1996	No data for determining crash risk
Waller(305)	1970	Review
West(306)	1968	No data for calculating crash risk
Wielgosz(307)	1993	Review
Ysander(308)	1969	Same data reported in Ysander(93) which is an included article

CMV Commercial motor vehicle.

CVD Cardiovascular disease.

MI Myocardial infarction.

Table D-2. Excluded Studies (Key Question 2)

Study	Year	Reason for Exclusion
Abdominal Aortic Aneurysms		
Alcorn et al.(35)	1996	Background information article
Allardice et al.(309)	1988	Study did not address rupture risk
Allen et al.(310)	1987	Letter to the editor
Almahameed et al.(134)	2005	Background information article

Study	Year	Reason for Exclusion
Bengtsson et al.(311)	1988	Background information article
Bengtsson et al.(97)	1991	Study did not examine risk of rupture
Bengtsson et al.(312)	1993	Study did not address rupture risk
Brady et al.(313)	2001	Background information article
Brady et al.(314)	2004	Background information article
Brewster et al.(135)	2003	Background information article
Castleden et al.(107)	1985	Background information article
Chang et al.(315)	1997	Study did not address risk of rupture
Cole et al.(316)	1989	Background information article
Collin et al.(317)	1988	Background information article
Cornuz et al.(118)	2004	Study did not address rupture risk; addressed risk of aneurysm development.
Cronenwett et al.(318)	1990	Data did not allow for risk of rupture calculation on the part of the authors.
Cronenwett JL(319)	2005	Background information article
Darling et al.(320)	1989	Study did not contain relevant data
Di Martino et al.(321)	2001	Background information article
Drott et al.(106)	1992	Study addressed incidence of rupture in population, but not risk.
Ehrlich et al.(322)	2002	Study did not contain relevant data
Elefteriades, JA(323)	1999	Letter to Editor
Fitzgerald et al.(324)	1995	Background information article
Fowkes et al.(109)	1989	Background information article
Gillum RF(111)	1995	Background information article
Gosling and Budge(325)	2003	Background information article
Grimshaw et al.(147)	1994	Background information article

Study	Year	Reason for Exclusion
Hallin et al.(152)	2001	Review paper
Harris et al.(141)	2000	Study addressed rupture postendovascular repair of aneurysm
Heikkinen et al.(326)	2002	Risk factors not adequately identified
Hirose et al.(327)	1992	Background information article
Isselbacher EM(101)	2005	Background information article
Johnson et al.(328)	1985	Background information article
Jones et al.(329)	2002	Background information article
Juvonen et al.(186)	1999	Study addressed risk associated with aortic dissection
Kalman et al.(330)	1999	Review article
Kanagasabay et al.(165)	1996	Background information article
Kazi et al.(331)	2003	Study did not address rupture risk
Lederle et al.(149)	1997	Study did not examine risk of rupture
Lederle et al.(150)	2003	Study does not define death by AAA as rupture, dissection, or both
Lederle et al.(126)	2000	Study examines for risk of aneurysm development, not for rupture risk
Lederle et al.(137)	2002	Study addresses issues of aneurysm repair
Li and Kleinstreuer(332)	2005	Background information article
Lilienfeld et al.(115)	1987	Background information article
Lilienfeld et al.(110)	1993	Background information article
Lindholt et al.(333)	1996	Background information article
Lovell et al.(334)	2006	Study did not address rupture risk; addressed risk of aneurysm development
MASS group(117)	2002	Background information article
Melton et al.(105)	1984	Study did not address rupture risk; addressed risk of aneurysm development
Naydeck et al.(335)	1999	Study did not address rupture risk

Study	Year	Reason for Exclusion
Naylor et al.(336)	1988	Background information article
Nicholls et al.(337)	1992	Background information article
O'Kelly and Heather(338)	1989	Background information article
Ogren et al.(339)	1996	Study did not examine risk of rupture
Ouriel et al.(340)	1992	Background reading
Pleumeekers et al.(341)	1995	Study addressed risk of aneurysm development
Powell and Brady(342)	2004	Background information article
Powell et al.(108)	1996	Background information article
Schermerhorn et al.(151)	2001	Review article
Schlatmann et al.(100)	1977	Study examined dissecting aorta only
Schurink et al.(142)	2000	Study did not examine rupture topic
Semenciw et al.(343)	1992	Study did not examine risk factors for rupture
Simoni et al.(144)	1996	Study did not examine risk of rupture
Simoni et al.(344)	1995	Study did not examine risk of rupture
Singh et al.(145)	2001	Study addressed incidence of rupture in population, but not risk
Spring et al.(99)	2006	Study did not address rupture risk; addressed risk of aneurysm development
Strachen, DP(345)	1991	Study did not address risk of rupture
Thompson, MM(133)	2003	Background information article
Tornwall et al.(148)	2001	Study examines for risk of aneurysm development, not for rupture risk
Vardaluki et al.(146)	2000	Study did not address rupture risk
Vardaluki et al.(346)	1998	Study did not provide rupture risk data, only estimates of rupture risk
Veith et al.(143)	2003	Background information article
Verloes et al.(347)	1995	Background information article
Vorp et al.(348)	2001	Study did not address rupture risk

Study	Year	Reason for Exclusion
Watt et al.(349)	1998	Study addressed risk of death from rupture, not risk of rupture itself
Wolf et al.(350)	1994	Background information article
Thoracic Aortic Aneurysms		
Bonser et al.(95)	2000	Study did not address rupture risk
Coady et al.(96)	1999	Review paper
Coady et al.(96)	1999	Background information article
Coady et al.(188)	1997	Review paper
Crawford et al.(351)	1991	Study did not include rates, only risks
Dapunt et al.(187)	1994	Natural history of disease paper
DeFrain et al.(189)	2006	Single case report
Ergin et al.(176)	1999	Paper on treatment recommendation
Gillum RF(111)	1995	Background information article
Gosling and Budge(325)	2003	Background information article
Hannuksela et al.(352)	2006	Study did not address rupture risk
Hirose et al.(327)	1992	Background information article
Isselbacher EM(101)	2005	Background information article
Johansson et al.(172)	1995	Background information article
Joyce et al.(353)	1964	Study of incidence rates only
Lilienfeld et al.(110)	1993	Background information article
Masuda et al.(102)	1992	Study did not examine rupture risk
Pressler and McNamara(354)	1980	Study did not provide risk information data
Rizzo et al.(166)	1998	Background information article
Safi and Taylor(177)	2003	Review paper

Study	Year	Reason for Exclusion
Wung and Aouizerat(174)	2004	Background information article
Yamauchi et al.(175)	2006	Background information article

AAA Abdominal aortic aneurysm.

Table D-3. Excluded Studies (Key Question 3)

Reference	Year	Reason for Exclusion
Occhetta et al.(355)	2003	Uncontrolled registry
Occhetta et al.(356)	2004	Single blinded randomized controlled trial. Less than 10 patients per arm (control arm: n = 9)
Petersen et al.(198)	1994	Not a randomized controlled trial
Shah et al.(357)	1999	Not a randomized controlled trial
Sheldon et al.(197)	1998	Not a randomized controlled trial
Raj et al.(358)	2003	Not a randomized controlled trial
Benditt et al.(359)	1997	Not a randomized controlled trial
Sra et al.(360)	1993	Not a randomized controlled trial
Ammirati et al.(361)	1998	Compares different pacing methods

Table D-4. Excluded Studies (Key Question 4)

Reference	Year	Reason for Exclusion
Anderson and Camm(362)	1994	Does not address risk of crash or loss of consciousness with ICD
Axtell et al.(266)	1990	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Baessler et al.(363)	2005	Did not address crash risk or risk of incapacitation with ICD
Bansch et al.(233)	2002	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question.
Bansch et al.(263)	1998	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question.
Bardy et al.(227)	2005	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question.

Reference	Year	Reason for Exclusion
Beauregard et al.(364)	1995	Study did not address key question. Study assessed views of individuals with an ICD who drove. Data on sudden death risk, syncope, or defibrillation occurrence was presented, but this was an estimate determined from the findings of other studies
Bigger et al.(240)	1997	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Binns and Camm(365)	2002	Review article
Bleakley et al.(366)	2003	Review article
Brandeolone(367)	1974	Review article
Buxton et al.(236-238,240)	1999	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Capoferri et al.(249)	2004	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Cambre and Silverman(368)	1993	Review article
Connolly et al.(230)	2000	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Dolinak(369)	2001	Case report
Edhag(370)	1969	Not relevant
Freedberg et al.(252)	2001	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Freedberg et al.(269)	1995	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Fogoros et al.(262)	1989	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Garcia-Moran et al.(251)	2002	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Gimble(371)	2004	Editorial review
Gorman(372)	1995	Review article
Grimm et al.(255)	1993	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question.
Gross et al.(257)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Hohnloser et al.(228)	2004	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Hook et al.(256)	1993	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Jenkins(265)	1995	Abstract

Reference	Year	Reason for Exclusion
Jung et al.(373)	1997	Review article
Jung et al.(374)	1996	Review article
Jung et al.(375)	1996	Survey of 46 national delegates of European Working Group on Cardiac Pacing. Data presented in article not reliable
Jung and Luderitz(376)	1996	Policy paper, no data for risks of crash or incapacitation
Kadish et al.(229)	2004	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Kou et al.(258)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Kuck et al.(234)	2000	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Kriatselis(377)	2002	Letter to the Editor
Larsen et al.(378)	1990	Abstract
Larson et al.(379)	1994	Study evaluated driving following VF or VT. Some individuals included in study received and ICD. Data from individuals who received an ICD not presented separately
Lau et al.(380)	2004	Clinical trial of antiarrhythmics versus ICD. No data for risk of crash or incapacitation
Levine et al.(259)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Lowenfals(381)	2002	Letter to the Editor
Maloney et al.(260)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Maron et al.(253)	2000	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Miles(382)	1997	Review article
Moss et al.(232)	2002	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Moss et al.(241)	1996	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Nademanee et al.(250)	2003	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Rupel et al.(254)	1998	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Sanchez et al.(267)	2006	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Schwerba(383)	2005	Discussion on guidelines, not risk of crash or incapacitation
Sears et al.(384)	1999	Discussion of quality of life issues, not risks for crash or incapacitation

Reference	Year	Reason for Exclusion
Shea(385)	2004	Discussion of quality of life issues, not risks for crash or incapacitation
Shoels(265)	1995	Abstract (same page in journal as Jenkins also(265)). Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Simpson et al.(243)	2004	Review and Canadian driving guidelines
Sowton(386)	1972	Review article. Not relevant to ICDs and crash risk
Strickberger(387)	1991	Review article. No original data on risk of crash or incapacitation
Tchou(388)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Tchou et al.(261)	1991	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Trappe et al.(389)	1998	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Wallace et al.(213)	2002	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Wever et al.(242)	1995	Studied incidence of relevant outcomes in patients with ICD but does not provide relevant outcome data for individuals while driving. Findings of study discussed in background section for key question
Wielgosz(307)	1993	Review article

ICD Implantable cardioverter defibrillator.

VF Ventricular fibrillation.

VT Ventricular tachycardia.

Table D-5. Excluded Studies (Key Question 5)

Study	Year	Reason for Exclusion
Bauer et al.(390)	2003	Review article
Berger et al.(391)	2005	Study addressed progressive pump failure death, but not sudden death. In addition, the study reported data from same patients as used in Berger et al. 2002.(283)
Burns et al.(392)	2002	Study did not address sudden death
Fuenmayor et al.(393)	2004	Study did not address LVEF.
Guzzetti et al.(394)	2005	Study addressed progressive heart death, but not sudden death
John et al.(395)	2004	Review article
Pruvot et al.(396)	2003	Review article

Study	Year	Reason for Exclusion
Santini et al.(397)	2001	Review article
Watanabe et al.(398)	2005	Study reported data from same patients as used in Watanabe et al. 2006.(275)
Zoni-Berisso et al.(399)	2001	Study did not assess the risk of sudden death or incapacitation in individuals with low LVEF

LVEF Left ventricular ejection fraction.

Table D-6. Excluded Studies (Key Question 6)

Study	Year	Reason for Exclusion
Adachi et al.(279)	2001	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Balanescu et al.(285)	2004	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Bauer et al.(390)	2003	Review article
Berger et al.(283)	2002	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Berger et al.(391)	2005	Study addressed progressive pump failure death, but not sudden death. In addition, the study reported data from same patients as used in Berger et al. 2002.(283)
Burns et al.(392)	2002	Study did not address sudden death
Buxton et al.(277)	2002	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Fuenmayor et al.(393)	2004	Study did not address LVEF.
Guzzetti et al.(394)	2005	Study addressed progressive heart death, but not sudden death
John et al.(395)	2004	Review article
La Rovere et al.(282)	2003	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Pedersen et al.(284)	2006	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Pruvot et al.(396)	2003	Review article
Raczak et al.(281)	2004	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Santini et al.(397)	2001	Review article
Sharir et al.(280)	2001	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Solomon et al.(276)	2005	Did attempt to determine whether the association between risk for sudden death or incapacitation and LVEF differs by the underlying etiology of heart failure
Watanabe et al.(275)	2006	Does not address key question.
Watanabe et al.(398)	2005	Study reported data from same patients as used in Watanabe et al. 2006.(275)
Zoni-Berisso et al.(399)	2001	Study did not assess the risk of sudden death or incapacitation in individuals with low LVEF.

LVEF Left ventricular ejection fraction.

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic reviews in that we provide two types of conclusions; qualitative conclusions and quantitative conclusions. In order to reach these conclusions, we use an algorithm developed by ECRI to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(52) The algorithm, which is presented in Figure E-3 through Figure E-6, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately the stability and strength-of-evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: (1) to assess the quality of each included study; and (2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Quality Scale I (for randomized and nonrandomized comparative studies), the ECRI Quality Scale III (for pre-post studies), and a revised version of the Newcastle-Ottawa Quality Assessment Scale (for case-control studies).(400) These instruments are presented in Appendix F.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question's specific evidence base into one of three distinct categories; high-, moderate- or low-quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EQS I Score	Median EQS III Score	Median NOQAS Score	Median EQS VI Score
High Quality	≥9.0			
Moderate Quality	6.0 to 8.9	≥9.0	≥8.0	≥8.0
Low Quality	≤6.0	<9.0	<8.0	<9.0

Decision Point 3: Quantitative Analysis Performed?

In this evidence report the answer to Decision Point 3 depended on a number of factors, which included the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least three studies must be available before a quantitative analysis will be considered. If 4 or more studies were available but poor reporting precluded ECRI from directly computing relevant effect-size estimates for >75% of the available studies, no quantitative analyses were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8, which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

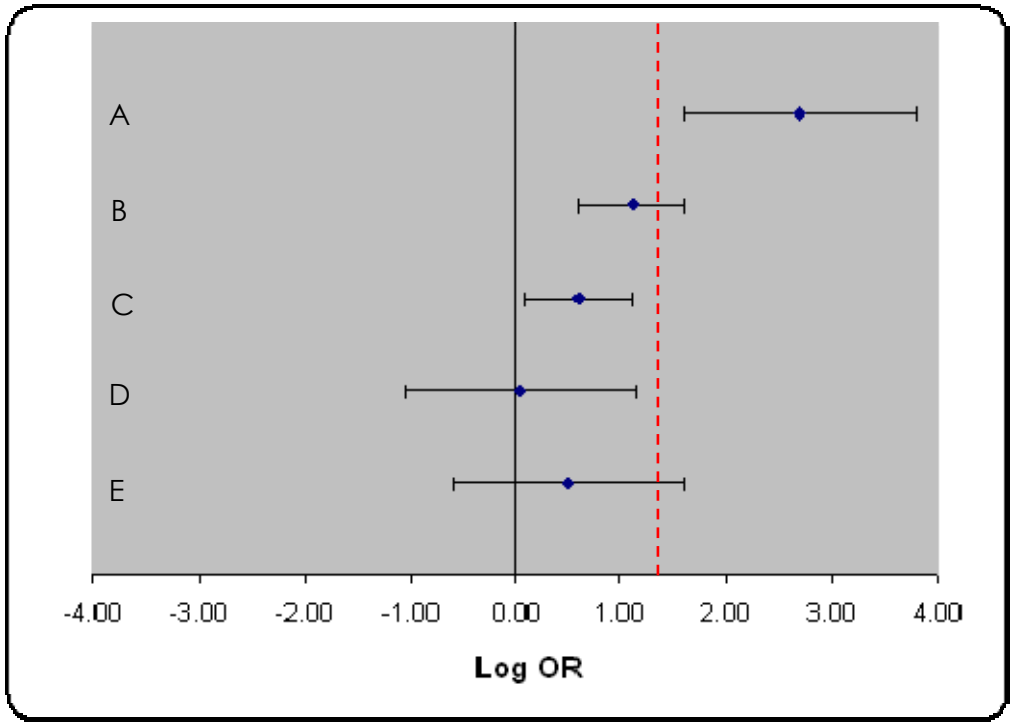
Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this evidence report we used both the Q-statistic and Higgins and Thompson's I^2 statistic.(9) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50% and *P*(Q) >0.10.

If the findings of the studies included were homogeneous (I^2 <50% and *P*(Q) >0.10), we obtained a summary effect-size estimate by pooling the results of these studies using FEMA. Having obtained a summary effect-size estimate, we then determined whether this effect size estimate was informative. That is, we determined whether the findings of the meta-analysis allowed a conclusion to

be drawn. To see what is meant by this, consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is noninformative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant, but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect, and it is also unclear whether the treatment effect is clinically important. This latter finding is thus noninformative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the FEMA were found to be informative, we next assessed the stability of the summary effect-size estimate obtained. Stability refers to the likelihood that a summary effect-size estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect-size estimate are known as sensitivity analyses. Clearly, one's confidence in the validity of a treatment effect estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect.

For this evidence report, we utilized four different sensitivity analyses. These sensitivity analyses include the following:

1. *Random-effects meta-analysis of complete evidence base.* When the quantitative analysis is performed on a subset of available studies, a random-effects meta-analysis that includes imprecise estimates of treatment effect calculated for all available studies will be performed. For this evidence report, the summary estimate of treatment effect determined by this analysis will be compared to the summary effect-size estimate determined by the original FEMA. If the random-effects effect-size estimate differs from the original FEMA by some prespecified tolerance, the original effect-size estimate will not be considered stable.

   The prespecified tolerance levels for each of the potential effect-size estimates we could have utilized in this evidence report are presented in Table E-2.

   Table E-2. Prespecified Tolerance Levels

Effect-Size Estimate	WMD	SMD	% of Individuals	RR	OR
Tolerance	±5%	±0.1	±5%	±0.05	±0.05

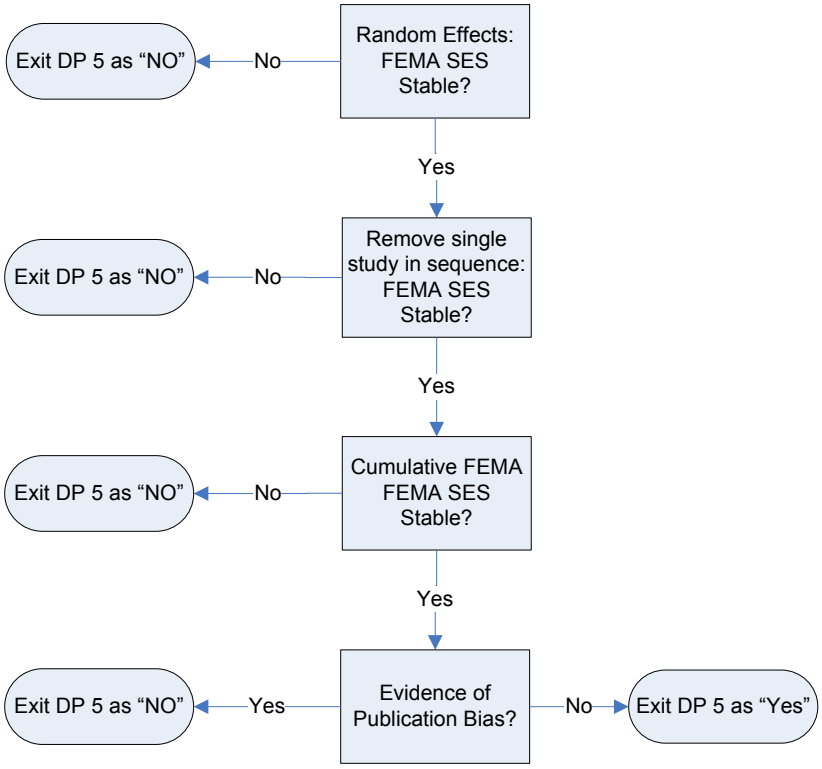
2. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.

3. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(13-15,65) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(14,15)estimates the number of unpublished studies (and their effect sizes). After the addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect-size estimate, adjusted for missing studies, differed from the pooled estimate of treatment effect determined by the original FEMA by >±5%, the we determined that the findings of our original analysis are not robust and the effect-size estimate is not stable.
4. *Cumulative FEMA.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect-size estimate. For this evidence report, we performed three different cumulative FEMAs:
    a. Studies were added in order of weight.
    b. Studies were added cumulatively to a FEMA by date of publication with the oldest study first.
    c. Studies were added cumulatively to a FEMA by date with the newest study first.

    In each instance, the pooled effect-size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect-size estimate effect of >±5%.

Because it is possible to reach Decision Point 6 with two different types of evidence bases (100% or <100% ≥75% of total available evidence bases), two slightly different sets of sensitivity analyses are needed. Figure E-2 shows the procedural algorithm that was used when dealing with these two types of evidence bases.

Figure E-2. Sensitivity Analysis Algorithm 1: Used when Original FEMA Utilized Data from All Available Studies



Decision Points 6 and 7: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a random-effects cumulative meta-analysis (cREMA). We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became nonsignificant as studies were added to

the evidence base). If the qualitative findings of the last three study additions were in agreement, then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example, one might ask, "When compared to insulin injection, do all included studies find that inhaled insulin is a significant risk factor for a motor vehicle crash?"

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones' qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be large cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect-size estimate is extremely large using a modified Delphi technique.

Figure E-3. General Section

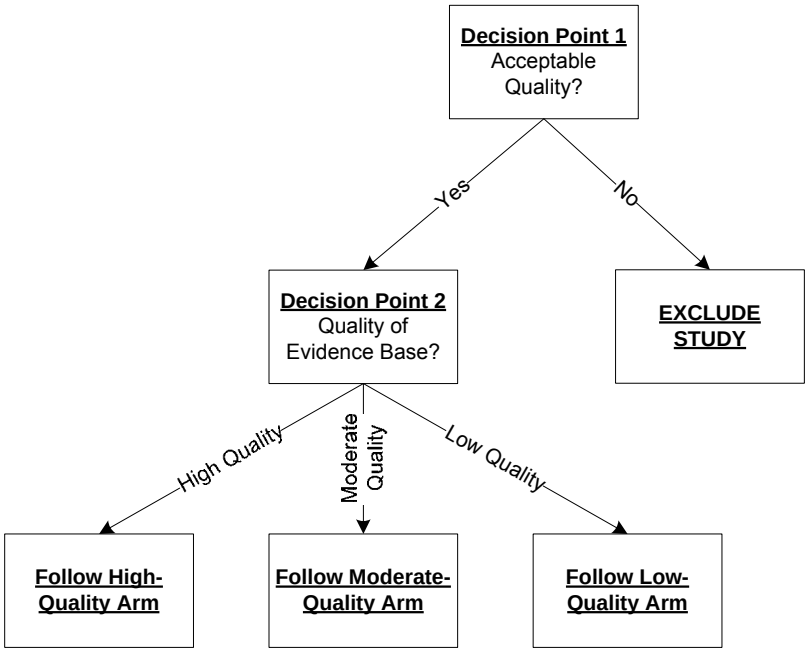


Figure E-4. High Quality Pathway

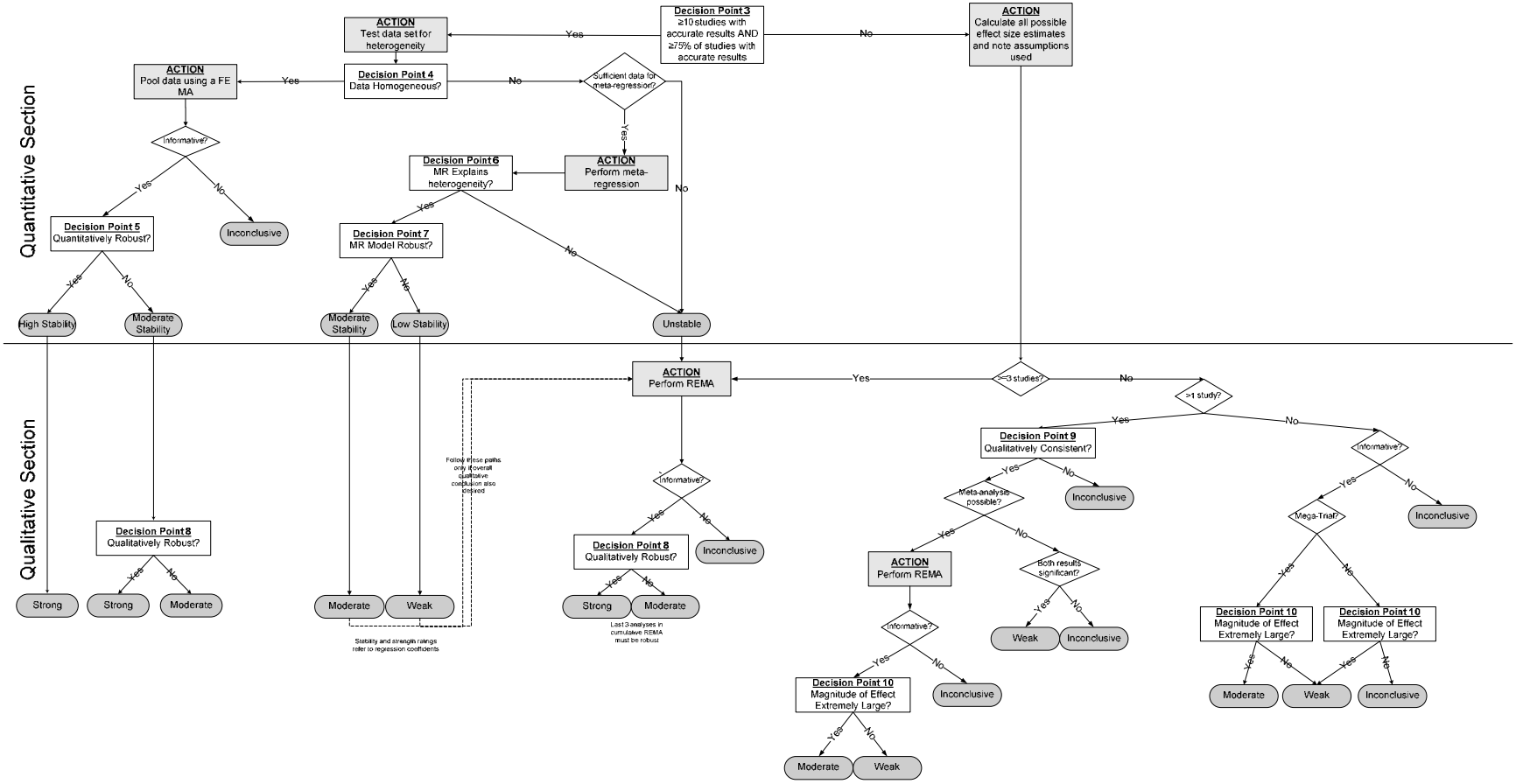


Figure E-5. Moderate Quality Pathway

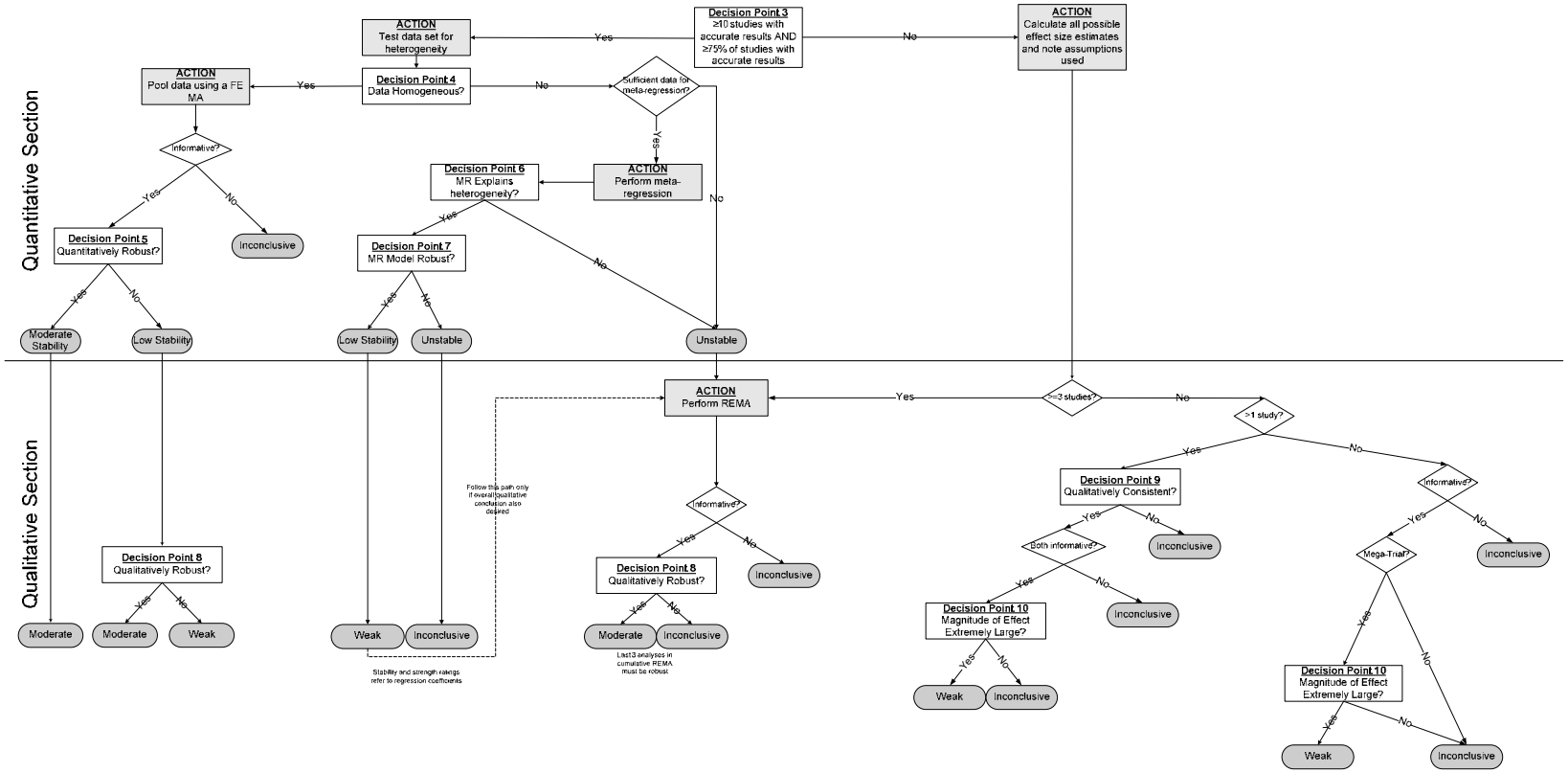
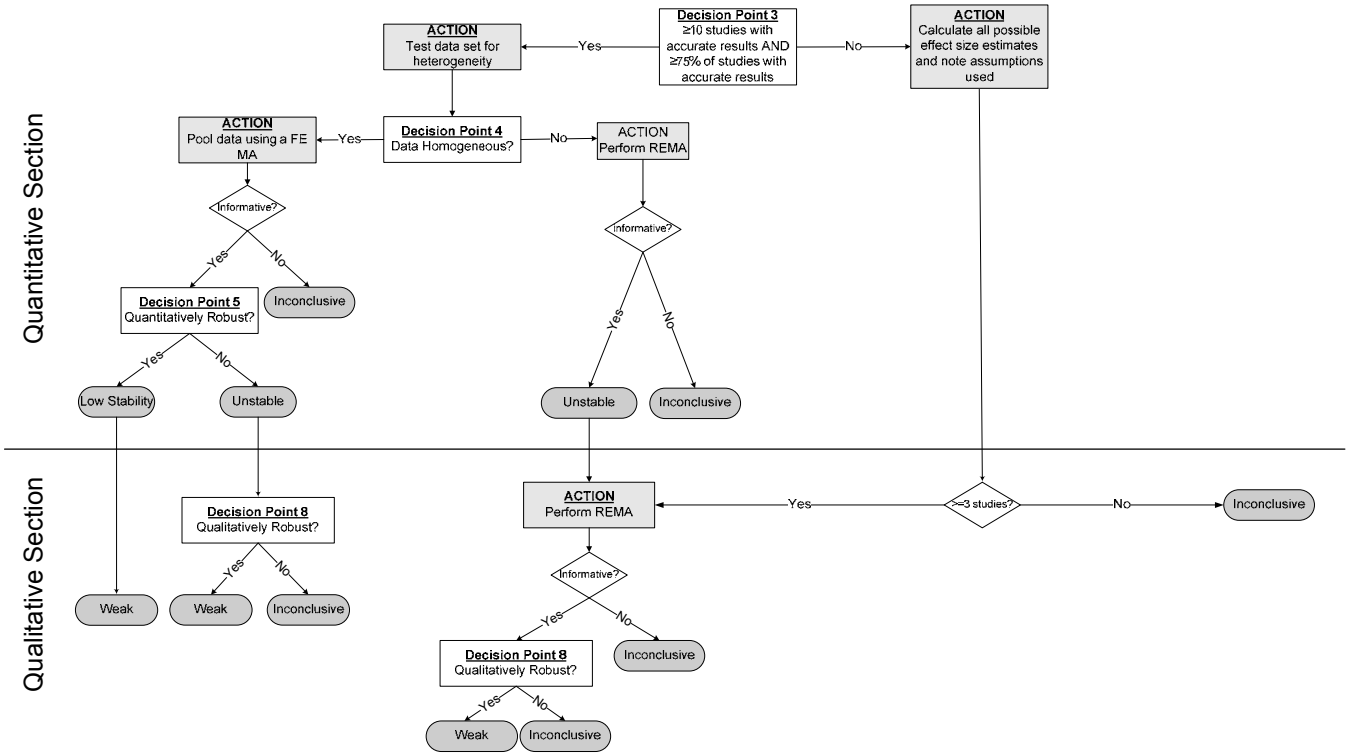


Figure E-6. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; ECRI Quality Scale I for comparative trials, ECRI Quality Checklist III for before-after studies, and a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(400)

ECRI Quality Scale I: Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study employ stochastic randomization?
3	Were any methods other than randomization used to make the patients in the study's groups comparable?
4	Were patients assigned to groups based on factors other than patient or physician preference?
5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
7	Was the comparison of interest prospectively planned?
8	Did ≥85% of the patients complete the study?
9	Was there a ≤15% difference in completion rates in the study's groups?
10	Were all of the study's groups concurrently treated?
11	Was compliance with treatment ≥85% in both of the study's groups?
12	Were all of the study's groups treated at the same center?
13	Were subjects blinded to the treatment they received?
14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
15	Was the treating physician blinded to the groups to which the patients were assigned?
16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
17	Was there concealment of allocation?
18	Was the outcome measure of interest objective **and** objectively measured?
19	Were the same laboratory tests, clinical findings, psychologic instruments, etc. used to measure the outcomes in all of the study's groups?
20	Was the instrument used to measure the outcome standard?
21	Was the same treatment given to all patients enrolled in the experimental group?
22	Was the same treatment given to all patients enrolled in the control group?
23	Were the follow-up times in all of the study's relevant groups approximately equal?
24	Was the funding for this study derived from a source that does not have a financial interest in its results?
25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section, supported by the data presented in the

Question #	Question
	articles results section?

ECRI Quality Scale III: Pre-Post Studies

Item	Question
1	Was the study prospective?
2	Did the study enroll all patients or consecutive patients?
3	Were the criteria for including and excluding patients based on objective laboratory and/or clinical findings?
4	Were the patient inclusion/ exclusion criteria established *a priori*?
5	Was the same initial treatment given to all patients enrolled?
6	Did all patients receive the same subsequent treatment(s)?
7	Was the outcome measure objective and objectively measured?
8	Did ≥85% of patients complete the study?
9	Were the characteristics of those who did and did not complete the study compared, and were these characteristics similar?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?
11	Were the author's conclusions, as stated in the abstract or the article's discussion section, supported by the data presented in the article's results section?

ECRI Quality Scale VI: Surveys

Item	Question
1	Were the questions developed from an expert group or focus group?
2	Was the pretest sample sufficiently large (>40 respondents)?
3	Were the characteristics of those who did not complete the study compared with those who completed the study, and were those characteristics similar?
4	Were the pretest sample respondents similar in characteristics to the study's respondents?
5	Were the respondents selected for the survey either consecutively or randomly?
6	Are the questions about crash (or other relevant outcome) not in the first 25% of the questions?
7	Does the questionnaire have reliability checks by asking the same question more than once but differently?
8	Were the respondents informed that their responses were confidential?
9	Were the conclusions as stated in the abstract and discussion consistent with the data presented in the results section?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of ten questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Question #	Question
1	Do the cases have independent validation?
2	Are the cases representative?
3	Are the controls derived from the community?
4	At the designated endpoint of the study, do the controls have the outcome of interest?
5	Does the study control for the most important confounder?
6	Does the study control for any additional confounders?
7	Was exposure/outcome ascertained through a secure record (surgical, etc.)?
8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
9	Was the same method of exposure/outcome ascertainment used for both groups?
10	Was the nonresponse rate of both groups the same?
11	Was the investigation time of the study the same for both groups?
12	Was the funding free of financial interest?
13	Were the conclusions supported by the data?

Appendix G: Study Summary Tables

Study Summary Tables (Key Question 1)

Crancer A, O'Neall P. A record analysis of Washington drivers with license restrictions for heart disease. Northwest Med 1970; 69(6): 409-16

Key Questions Addressed	1	2	3	4	5
	✓				

Research Question	To determine if there are drivers with specific heart diseases, masked by the over-all heart disease group, that have significantly higher crash, violation, or crash and violation rates than those of a comparable non-restricted population. Findings among patients with and without pacemakers were compared.	
Study Design	Retrospective case-controlled record review	
Population	**Inclusion Criteria**	Washington state licensed drivers with heart disease. Study (n=474) and case controls (n=473) matched for gender, age (within 5 years), and city of residence. Time frame 7/1963 – 7/1969.
	Exclusion Criteria	None reported
	Study population characteristics	Variable / Values n: 947; 44 with pacemakers Age: (yrs.) median: 60 yrs Height (cm) mean ±SD: Not reported Weight (kg) mean ±SD: Not reported Gender M/F: Not reported
	Generalizability to CMV drivers	Unclear. Patients in this sample may be older, and do not necessarily drive a commercial vehicle. The data are old, and treatments have changed since then. Drivers in this sample are from Washington State only.
Methods	Stratified random samples, generated with a random number table, were selected from drivers with medically restricted licenses. Controls were non-restricted drivers matched based upon gender, age, and city of residence. The number of/combined number of crashes, and violations were compared.	
Statistical Methods	Not reported	

Quality Assessment

Internal Validity	1	2	3	4	5	6	7	8	9	10	11	12	13
	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y
Score = 7.7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Category= Moderate	**27**	**28**											

Relevant Outcomes Assessed	Number of crashes, violations, and combined number of crashes and violations over time
Results	See Table G-1 through Table G-10: Drivers in the arteriosclerotic and hypertensive groups had

	statistically significantly higher crash rates than matches. Among drivers with restrictions due to rheumatic or other heart disease, or with hypertension, there was no important difference as compared to controls. There were no significant differences in injury or fatal crashes for any matched disease-control pair group.
Authors' Comments	The arteriosclerotic and hypertensive disease groups each were found to have significantly higher crash rates than that of their matched groups. The remaining two groups, rheumatic and other heart disease, were not significantly different from their matched groups in terms of crash rates. None of the violation rates for any of the four disease groups were significantly different from their matched groups.

Table G-1. Crash and Violation Rates*: Heart Disease and Matched Groups

	Crashes		Violations		Crashes and Violations	
Disease Type	Disease Group Mean	Matched Group Mean	Disease Group Mean	Matched Group Mean	Disease Group Mean	Matched Group Mean
Arteriosclerotic	.35	.18	.59	.67	.94	.85
Hypertensive	.31	.13	.51	.38	.82	.51
Rheumatic	.21	.25	.47	.68	.68	.93
Other Heart Disease	.24	.17	.69	.76	.92	.93

*Driving record includes time period July 1963 - July 1969.

Table G-2. Crash and Violation Rates*: Pacemaker, Matched Pacemaker, and Heart Disease Groups

Group	Crashes	Violations	Crashes and Violations
Pacemaker	.25	.64	.89
Matched Pacemaker	.18	.32	.50
Heart Disease	.39	.36	.75

*Driving record includes time period July 1963 – July 1969.

Table G-3. Percentage Distribution of the Number of Crashes*: Heart Disease and Matched Groups

Number of Crashes	Arteriosclerotic***		Hypertensive***		Rheumatic		Other Heart Disease	
	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group
0	70.92	85.82	76.27	87.50	81.18	81.18	78.46	86.61
1	23.40	9.93	18.64	11.67	16.47	14.12	20.00	11.02
2	4.96	4.26	3.39	.83	2.35	3.53	.77	1.57
3	4.96	4.26	.85			1.18	.77	.79
4			.85					
5								
Total**	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Total Drivers	141	141	118	120	85	85	130	127

*Driving record includes time period July 1963 – July 1969.

**Due to rounding, columns may not add to 100.

***The distribution of crashes differs significantly between the disease and matched groups (p<.05).

Table G-4. Percentage Distribution of the Number of Crashes*: Pacemaker, Matched Pacemaker, and Heart Disease Groups

Number of Crashes	Pacemaker	Matched Pacemaker	Heart Disease
0	79.55	81.82	75.00
1	15.91	18.18	13.64
2	4.55		9.09
3			2.27

Total**	100.00	100.00	100.00
Total Drivers	44	44	44

*Driving record includes time period July 1963 – July 1969.

** Due to rounding, columns may not add to 100.

Table G-5. Percentage Distribution of the Number of Violations*: Heart Disease and Matched Groups

	Arteriosclerotic		Hypertensive		Rheumatic***		Other Heart Disease	
Number of Violations	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group
0	67.38	70.21	67.80	71.67	65.88	62.35	61.54	58.27
1	19.15	15.60	23.73	20.83	27.06	17.65	23.85	25.20
2	9.22	2.84	5.08	5.83	2.35	12.94	4.62	10.24
3	1.42	4.96	.85	1.67	3.53	4.70	7.69	1.57
4	.71	3.55	.85		1.18	1.18	.77	1.57
5	.71	2.13	.85			1.18		
6							.77	2.36
7	.71						.77	.79
8	.71	.71	.85					
Total**	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Total Drivers	141	141	118	120	85	85	130	127

*Driving record includes time period July 1963 – July 1969.

** Due to rounding, columns may not add to 100.

***The distribution of violations differ significantly between the disease and matched groups ($p < .05$).

Table G-6. Percentage Distribution of the Number of Violations*: Pacemaker, Matched Pacemaker, and Heart Disease Groups

Number of Violations	Pacemaker	Matched Pacemaker	Heart Disease
0	68.18	77.27	79.55
1	18.18	15.91	11.36
2	6.82	4.55	4.55
3	2.27	2.27	2.27
4+	4.55		2.27
Total	100.00	100.00	100.00
Total Drivers	44	44	44

*Driving record includes time period July 1963 – July 1969.

Table G-7. Percentage Distribution of the Number of Crashes and Violations*: Heart Disease and Matched Groups

Number of Violations And Crashes	Arteriosclerotic		Hypertensive		Rheumatic		Other Heart Disease	
	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group
0	52.48	63.12	58.47	67.50	56.47	56.47	50.77	55.12
1	24.82	19.15	21.19	19.17	29.41	14.12	29.23	23.62
2	10.64	4.96	11.86	9.17	7.06	16.47	7.69	11.02
3	7.09	3.55	3.39	3.33	4.71	8.24	4.62	3.94
4	2.84	5.67	3.39	.83	1.18	2.35	6.15	1.57
5	.71	2.13	.85		1.18	2.35		.79
6							.77	2.36
7	.71	.71					.77	1.57
8								
9								
10	.71	.71						

11			.85					
Total**	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Total Drivers	141	141	118	120	85	85	130	127

*Driving record includes time period July 1963 – July 1969.

** Due to rounding, columns may not add to 100.

Table G-8. Percentage Distribution of the Number of Crashes and Violations*: Pacemaker, Matched Pacemaker, and Heart Disease Groups

Number of Violations and Crashes	Pacemaker	Matched Pacemaker	Heart Disease
0	63.64	70.45	59.09
1	13.64	15.91	25.00
2	11.36	9.09	6.82
3	4.55	2.27	4.55
4+	6.82	2.27	4.55
Total**	100.00	100.00	100.00
Total Drivers	44	44	44

*Driving record includes time period July 1963 – July 1969.

** Due to rounding, columns may not add to 100.

Table G-9. Distribution of Crashes by Type*

	Arteriosclerotic		Hypertensive		Rheumatic		Other Heart Disease	
	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group	Disease Group	Matched Group
Fatal Crashes	0	0	0	0	0	0	0	0
Injury Crashes	7	3	3	3	5	4	2	4
Injuries	14	3	3	3	12	7	2	8
Number of Crashes	50	26	37	16	18	21	31	21
Number of Drivers	141	141	118	120	85	85	130	127

*Driving Record includes time period July 1963 through July 1969.

Table G-10. Distribution of Crashes by Type: Pacemaker, Matched Pacemaker, and Heart Disease Group

Type of Crash	Pacemaker	Matched Pacemaker	Heart Disease
Fatal	0	0	0
Injury	2	3	5
Number of Injuries	2	4	5
Number of Crashes	11	8	17
Number of Drivers	44	44	44

* Driving Record includes time period July 1963 through July 1969.

Crancer A, McMurray L. Crash and violation rates of Washington's medically restricted drivers. JAMA 1968; 205:74-78														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
	✓													
Research Question	To compare crash and violation rates of medically restricted drivers (with conditions stable for at least 3 months) in Washington state with those of all motorists licensed in Washington state.													
Study Design	Retrospective case-control records review													
Population	**Inclusion Criteria**	Washington state drivers with medically restricted licenses (20,710 total), including heart disease (n=7,416) during 1/1/61 – 10/1/67												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable	Values											
		n	20,714 (7,416 with CVD)											
		Age: (yrs.) mean ±SD	Not reported											
		Height (cm) mean ±SD	Not reported											
		Weight (kg) mean ±SD	Not reported											
		Gender M/F	Not reported											
	Generalizability to CMV drivers	Unclear. Greater representation of men and older people in this sample than in the general driving population. All drivers were in Washington state, and they did not necessarily operate a commercial vehicle.												
Methods	Crash and violation rates for drivers with and without heart disease license restrictions were compared between gender and age groups, using records from Jan. 1961 to Oct. 1, 1967.													
Statistical Methods	A nonparametric sign test was used to compare age groups of men and women with the corresponding groups in the population. Next, a parametric test making use of the central limit theorem was used to compare the crash rates of the same group to those of the populations. If both approaches agreed in rejecting the null hypothesis at 5% level, a statistical difference was reported. Otherwise, the difference was either higher or lower.													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y
	Score = 8	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes, traffic violations over time													
Results	Drivers with heart disease had a violation rate statistically lower than gender and age-matched population of general population of Washington state licensed drivers. Their crash rate was greater, but not statistically significant.													
Authors' Comments	Limitations of this study include generalizability of the sample to all drivers and a possible failure of people to properly register for medically restricted licenses.													

Table G-11. A Comparison of Crash and Violation Rates: Restricted Groups and Population

	Crashes Per 100*		Violations Per 100*	
Group With Restrictions	**Observed Group**	**Population†**	**Observed Group**	**Population†**
License Restrictions				
Diabetes	31.45	26.5	73.33	68.53
Epilepsy	41.4	31.06	110.09	95.55
Fainting	49.42	27.03	98.85	74.15
Heart	25.87	25.28	50.32	56.56
Other	32.75	26.32	79.85	46.21
Vision	25.4	25.48	56.02	57.36
Driving restrictions	32.27	28.72	88.97	87.17

* Average per 100 drivers for the period Jan 1, 1961 to Oct 1, 1967.

† Based on a population with an age distribution comparable to that of each group of drivers with restrictions

Table G-12. Crash and Violation Rates for Drivers with a Heart Disease License Restriction

	Women		Men		Men and Women	
Ages (Yr)	**Total Drivers**	**Average Per 100***	**Total Drivers**	**Average Per 100***	**Total Drivers**	**Average Per 100***
Crashes						
13-17	7	14.29	21	. . .	28	3.57
18-20	15	26.67	27	37.04	42	33.33
21-25	9	. . .	29	51.72	38	39.47
26-30	14	14.29	15	80	29	48.28
31-35	29	6.89	24	50	53	26.41
36-50	460	8.04	788	32.86	1,248	23.71
51-65	765	15.03	2,477	31.61	3,242	27.69
66 & older	592	14.86	2,144	27	2,736	24.37
Total	**1,891**	**13.16**	**5,525**	**30.22**	**7,416**	**25.87**
Violations						
13-17	7	. . .	21	57.14	28	42.86
18-20	15	26.67	27	222.22	42	152.38
21-25	9	11.11	29	196.55	38	152.63
26-30	14	35.71	15	166.67	29	103.45
31-35	29	31.03	24	116.66	53	69.81
36-50	460	12.6	788	83.24	1,248	57.21
51-65	765	28.36	2,477	63.5	3,242	55.21
66 & older	592	21.21	2,144	42.07	2,736	37.53

Total	**1,891**	**22.15**	**5,525**	**59.96**	**7,416**	**50.82**

* Average per 100 drivers for the period Jan 1, 1961 to Oct 1, 1967.

Davis T, Wehling E, Carpenter R. Oklahoma's medically restricted drivers. A study of selected medical conditions. J Okla State Med Assoc. 1973 Jul; 66(7): 322-7														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
	✓													
Research Question	To attempt to reduce the Oklahoma highway death toll by reviewing fitness of individuals with certain medical conditions to drive.													
Study Design	Record review by the Oklahoma Medical Society (OMAC) of medically restricted drivers with moving violations (including speeding) and crashes during 1970													
Population	**Inclusion Criteria**	All drivers with diabetes; cardiac or circulatory conditions; epilepsy; neurological disorder such as stroke or chronic brain syndrome [dementia]; granted drivers licenses after being reviewed by the OMAC in 1969.												
	Exclusion Criteria	Persons with revoked or suspended licenses during the time frame; counts of moving violations for which no conviction was made.												
	Study population characteristics	Variable n Age: (yrs.) mean ±SD Height (cm) mean ±SD Weight (kg) mean ±SD Gender M/F	Values 318 restricted drivers Not reported (20% of patients were >65 years old and 43% were <24 years old) Not reported Not reported 70% M											
	Generalizability to CMV drivers	Unclear. As with CMV drivers there was a predominance of males in this study (almost 70%). Oklahoma drivers only.												
Procedures	Crashes and moving violations were identified using state records for individuals with medically restricted driver's licenses. Violations were categorized by chronic disease type and compared to those of all licensed Oklahoma drivers.													
Statistical Methods	N/A													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y
	Score = 9.4	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= High	**27**	**28**											
Relevant Outcomes Assessed	Number of moving driving violations and crashes by chronic disease type													
Results	Table G-13., Table G-14, Table G-15, and Table G-16: Males in the cardiac and circulatory category had a crash rate slightly higher than the rate for all licensed males. The crash rate of each age group, for which a rate could be calculated, was also slightly higher than that of the matched age group. The violation rate was slightly lower than that for the overall population. The 65+ age group accounted for the majority of crashes and violations. As a group, females in the cardiac and circulatory category had a violation rate considerable lower than the overall rate. No crashes were													

	recorded for females in this category.
Authors' Comments	The cardiac and circulatory group had the highest percentage of persons not involved in a known moving violation during 1970. Other selected chronic diseases were diabetes, epilepsy, and other neurological.

Table G-13. Distribution of Violations for Selected Chronic Diseases

Number of Violations	Diabetes		Cardiac and Circulatory		Epilepsy		Other Neurological	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
0	79	73.15	47	85.45	57	74.08	60	76.92
1	24	22.22	5	9.09	13	16.88	9	11.54
2	0	0.00	2	3.64	5	6.49	6	7.69
3	4	3.70	1	1.82	1	1.80	0	0.00
4+	1	0.93	0	0.00	1	1.30	3	5.65
Totals	**108**		**55**		**77**		**78**	

Table G-14. Distribution of Crashes for Selected Chronic Diseases

Number of Violations	Diabetes		Cardiac and Circulatory		Epilepsy		Other Neurological	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
0	101	93.52	50	90.91	65	84.41	68	87.18
1	6	5.56	5	9.09	10	12.98	8	10.25
2	1	0.92	0	0.00	2	2.61	2	2.57
3+	0	0.00	0	0.00	0	0.00	0	0.00
Totals	**108**		**55**		**77**		**78**	

Table G-15. Moving Violation Rates for Selected Conditions in "Medically Handicapped" Oklahoma Drivers in 1970*

	Male	Female	Male & Female
Diabetes	49.2	20.9	38.0
Cardiac & Circulatory	24.4	14.3	21.8
Epilepsy	49.0	19.3	39.0
Other Neurological	50.8	15.4	42.3
All Licensed Oklahoma Drivers			26.4

* Violations per 100 drivers

Table G-16. Crash Rates for Selected Conditions in "Medically Handicapped" Oklahoma Drivers in 1970*

	Male	Female	Male & Female
Diabetes	9.2	4.7	7.4
Cardiac & Circulatory	12.2	0.0	9.1
Epilepsy	23.5	7.7	18.2
Other Neurological	10.8	30.8	14.1
All Licensed Oklahoma Drivers	8.7	4.8	7.1

* Crashes per 100 drivers

Dionne G, Desjardins D, Laberge-Nadeau C, Maag U. Medical conditions, risk exposure, and truck drivers' crashes: An analysis with count data regression models. Accid Anal and Prev 1995; 27: 295-305														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
	✓													
Research Question	To assess the effect of different medical conditions, including cardiovascular disease, on truck drivers' distributions of crashes													
Study Design	Nested case-control													
Population	**Inclusion Criteria**	Male drivers aged 25+ years old and registered in Quebec, Canada, who drove a truck at work and had class 1 (articulated truck) or class 3 (rigid truck) permits												
	Exclusion Criteria	Drivers for whom not all data was available												
	Study population characteristics	Variable	Values											
		n	1,307											
		Age: (yrs.) mean ±SD	NR											
		Height (cm) mean ±SD	NR											
		Weight (kg) mean ±SD	NR											
		Gender M/F	100% M											
	Generalizability to CMV drivers	Study limited to drivers of commercial vehicles.												
Procedures	Data collected in 1989 was from a sample of 1,307 men who drove trucks as part of their employment. Data included information on permits, crashes, violations, "demerit points," medical conditions (for drivers who had to undergo a medical examination by regulation) and mileage (collected by phone survey).													
Statistical Methods	Poisson and negative binomial count data regression models for the number of crashes per year to assess the importance of health status, age, and exposure (miles driven)													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
	Score = 7.7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crash rates over time													
Results	Drivers in a [permit-holding] class other than Class 1 with the medical condition diabetes have more crashes that those in good health in the same class. There are no differences between the drivers with different medical conditions in Class 1; (Table G-17) (Table G-18) (Table G-19).													
Authors' Comments	One observes that most coefficients of the medical conditions are not statistically significant. This may be because the risk exposure is not well controlled in [statistical] Model 1.													

Table G-17. Estimated Count Regression Models for the Number of Crashes with a Truck per Year (Models 1 and 2)

	Model 1		Model 2	
Explanatory variables	Coefficient	*t*-statistic	Coefficient	*t*-statistic
Intercept	−2.41	−7.58 **	−2.33	−7.32 **
Alpha	2.25	4.08 **	2.19	4.04 **
Observation period				
1987	−0.31	−1.77 *	−0.29	−1.69 *
1988	−0.22	−1.29	−0.21	−1.26
1989	−0.24	−1.44	−0.24	−1.42
1990	omitted category		omitted category	
Permit class				
class 1	0.79	2.86 **	0.64	2.26 **
class others	omitted category		omitted category	
Age group				
25 years or less	omitted category		omitted category	
26 to 30	0.01	0.04	0.06	0.20
31 to 35	−0.35	−1.16	−0.28	−0.91
36 to 40	−0.72	−2.31 **	−0.63	−2.03 **
41 to 45	−0.46	−1.56	−0.36	−1.21
46 to 50	−0.82	−2.74 **	−0.74	−2.46 **
51 to 55	−0.85	−2.78 **	−0.76	−2.46 **
56 to 60	−0.71	−2.17 **	−0.61	−1.84 *
more than 60 years	−0.46	−1.12	−0.30	−0.73
Class 1—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.18	0.74	0.17	0.71
Coronary disease	0.26	1.16	0.24	1.10
Hypertension	−0.39	−1.58	−0.39	−1.57
No evaluation	−0.26	−1.19	−0.26	−1.20
Class others—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.86	2.60 **	0.84	2.53 **
Coronary disease	−0.51	−0.80	−0.53	−0.83
Hypertension	0.34	0.95	0.35	0.96
Visual impairment	0.34	1.05	0.37	1.15
No evaluation	−0.14	−0.34	−0.11	−0.26
Class 1—Owner of the truck				
Yes			−0.04	−0.22
No			omitted category	
Class others—Owner of the truck				
Yes			−0.77	−2.44 **
No			omitted category	
Numer of driver-years	4 099		4 099	
Number of variables	23		25	
Log-Likelihood	−1 124.27		−1 120.84	
Log-Likelihood Ratio Test (vs Model 1)			$\chi^2_2 = 6.86$ **	

*Significant at 10%.
**Significant at 5%.

Table G-18. Estimated Count Regression Models for the Number of Crashes with a Truck per Year (Models 3 and 4)

Explanatory variables	Model 3 Coefficient	Model 3 *t* statistic	Model 4 Coefficient	Model 4 *t* statistic
Intercept	−3.25	−7.32 **	−1.82	−3.89 **
alpha	1.81	3.76 **	1.88	3.82 **
Observation period				
1987	−0.30	−1.72 *	−0.31	−1.80 *
1988	−0.21	−1.24	−0.21	−1.24
1989	−0.25	−1.47	−0.25	−1.46
1990	omitted category		omitted category	
Permit class				
Class 1	0.79	1.78 *	−0.31	−0.66
Class others	omitted category		omitted category	
Age group				
25 years or less	omitted category		omitted category	
26 to 30	0.05	0.18	0.06	0.19
31 to 35	−0.25	−0.84	−0.30	−0.98
36 to 40	−0.64	−2.09 **	−0.64	−2.02 **
41 to 45	−0.43	−1.44	−0.42	−1.38
46 to 50	−0.75	−2.51 **	−0.74	−2.43 **
51 to 55	−0.70	−2.28 **	−0.72	−2.33 **
56 to 60	−0.56	−1.73 *	−0.57	−1.73 *
More than 60 years	−0.31	−0.76	−0.35	−0.86
Class 1—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.08	0.35	0.22	0.91
Coronary disease	0.18	0.83	0.27	1.20
Hypertension	−0.37	−1.51	−0.34	−1.36
No evaluation	−0.17	−0.78	−0.20	−0.94
Class others—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.83	2.53 **	0.87	2.56 **
Coronary disease	−0.40	−0.63	−0.54	−0.84
Hypertension	0.35	0.96	0.35	0.95
Visual impairment	0.34	1.07	0.38	1.17
No evaluation	−0.14	−0.33	−0.06	−0.14
Class 1—Distance driven				
≤ 15 000 km	omitted category			
15,001 to 40,000	0.69	2.93 **		
40,001 to 87,500	1.09	4.61 **		
> 87 500 km	1.13	4.92 **		
Class others—Distance driven				
≤ 10 000 km	omitted category			
10 001 to 22 500	0.75	1.89 *		
22 501 to 40 000	0.80	2.05 **		
> 40 000 km	1.14	3.04 **		
Class 1—Pull a trailer				
Always or often			0.08	0.44
Rarely or never			omitted category	
Class others—Pull a trailer				
Always or often			0.13	0.38
Rarely or never			omitted category	
Class 1–Drive after 8 PM				
Very often or often			−0.26	−1.47
Seldom or never			omitted category	
Class others—Drive after 8 PM				
Very often or often			−0.58	−1.73 *
Seldom or never			omitted category	
Class 1—Working radius				
Less than 50 km			omitted category	
Between 50–160 km			0.76	3.88 **
More than 160 km			0.82	3.49 **

Explanatory variables	Model 3 Coefficient	Model 3 t statistic	Model 4 Coefficient	Model 4 t statistic
Class others—working radius				
Less than 50 km			−0.65	−1.76 *
Between 50–160 km			−0.54	−1.44
More than 160 km			omitted category	
Class 1—Type of road				
Highways			−0.29	−1.15
Country roads			−0.30	−1.26
City streets			omitted category	
Highways & country roads			0.17	0.65
City streets & country roads			−0.22	−0.67
City streets & highways			0.06	0.23
Class others—Type of road				
Highways			−0.01	−0.02
Country roads			−0.20	−0.63
City streets			omitted category	
Highways & country roads			0.12	0.27
City streets & country roads			−0.62	−1.12
City streets & highways			0.14	0.41
Number of driver-years	4 099		4 099	
Number of variables	29		41	
Log-Likelihood	−1 103.03		−1 105.01	
Log-Likelihood Ratio Test (vs Model 1)	$\chi^2_6 = 42.48$**		$\chi^2_{18} = 38.52$**	

*Significant at 10%.
**Significant at 5%.

Table G-19. Estimated Count Regression Models for the Number of Crashes with a Truck per Year (Models 5 and 6)

Explanatory variables	Model 5 Coefficient	Model 5 *t* statistic	Model 6 Coefficient	Model 6 *t* statistic
Intercept	−2.70	−4.63 **	−3.26	−5.11 **
alpha	1.55	3.53 **	1.43	3.41 **
Observation period				
1987	−0.29	−1.68 *	−0.28	−1.65 *
1988	−0.20	−1.21	−0.19	−1.16
1989	−0.25	−1.49	−0.24	−1.46
1990	omitted category		omitted category	
Permit class				
Class 1	0.08	0.14	0.30	0.46
Class others	omitted category		omitted category	
Age group				
25 years or less	omitted category		omitted category	
26 to 30	0.09	0.31	0.13	0.43
31 to 35	−0.18	−0.59	−0.09	−0.29
36 to 40	−0.55	−1.76 *	−0.49	−1.54
41 to 45	−0.36	−1.19	−0.27	−0.89
46 to 50	−0.66	−2.16 **	−0.60	−1.96 **
51 to 55	−0.55	−1.77 *	−0.48	−1.54
56 to 60	−0.40	−1.20	−0.33	−0.98
More than 60 years	−0.15	−0.36	−0.14	−0.34
Class 1—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.12	0.51	0.12	0.51
Coronary disease	0.18	0.80	0.16	0.73
Hypertension	−0.34	−1.37	−0.36	−1.45
No evaluation	−0.17	−0.78	−0.14	−0.66
Class others—Medical conditions				
Good health	omitted category		omitted category	
Diabetes	0.78	2.31 **	0.84	2.42 **
Coronary disease	−0.49	−0.76	−0.36	−0.55
Hypertension	0.36	0.98	0.29	0.79
Visual impairment	0.38	1.17	0.43	1.30
No evaluation	−0.04	−0.10	−0.08	−0.18
Class 1—Owner of the truck				
Yes	−0.04	−0.22	−0.05	−0.26
No	omitted category		omitted category	
Class others—Owner of the truck				
Yes	−0.78	−2.45 **	−0.78	−2.40 **
No	omitted category		omitted category	
Class 1—Distance driven				
≤ 15 000 km	omitted category		omitted category	
15001 to 40000	0.64	2.69 **	0.57	2.37 **
40001 to 87500	0.99	3.98 **	0.90	3.57 **
> 87 500 km	1.22	4.52 **	1.08	3.97 **
Class others—Distance driven				
≤ 10 000 km	omitted category		omitted category	
10 001 to 22 500	0.68	1.69 **	0.30	1.45
22 501 to 40 000	0.82	2.05 **	0.21	1.50
> 40 000 km	1.05	2.66 **	0.74	1.81 *
Class 1—Pull a trailer				
Always or often	0.02	0.11	0.03	0.19
Rarely or never	omitted category		omitted category	
Class others—Pull a trailer				
Always or often	0.14	0.40	0.13	0.37
Rarely or never	omitted category		omitted category	
Class 1–Drive after 8 PM				
Very often or often	−0.27	−1.53	−0.26	−1.48
Seldom or never	omitted category		omitted category	

Table 5. Continued

Explanatory variables	Count data regression			
	Model 5		Model 6	
	Coefficient	t statistic	Coefficient	t statistic
Class others—Drive after 8 PM				
Very often or often	−0.58	−1.73 *	−0.65	−1.92 *
Seldom or never	omitted category		omitted category	
Class 1—Working radius				
Less than 50 km	omitted category		omitted category	
Between 50–160 km	0.62	3.13 **	0.58	2.90 **
More than 160 km	0.42	1.68 **	0.34	1.38
Class others—Working radius				
Less than 50 km	−0.30	−0.78	−0.13	−0.32
Between 50–160 km	−0.39	−1.03	−0.30	−0.76
More than 160 km	omitted category		omitted category	
Class 1—Type of road				
Highways	−0.50	−1.94 *	−0.50	−1.94 *
Country roads	−0.39	−1.58	−0.38	−1.55
City streets	omitted category		omitted category	
Highways & country roads	−0.04	−0.14	−0.03	−0.10
City streets & country roads	−0.29	−0.90	−0.29	−0.90
City streets & highways	−0.02	−0.08	0.02	0.07
Class others—Type of road				
Highways	−0.06	−0.16	0.03	0.06
Country roads	−0.17	−0.52	−0.17	−0.53
City streets	omitted category		omitted category	
Highways & country roads	0.06	0.14	0.10	0.22
City streets & country roads	−0.59	−1.05	−0.42	−0.74
City streets & highways	0.07	0.22	−0.01	−0.04
Class 1—Number of hours				
≤ 720 hrs			omitted category	
721 to 1 200			0.24	0.99
1 201 to 1 728			0.62	2.72 **
> 1 728 hrs			0.49	2.07 **
Class others—Number of hours				
≤ 585 hrs			omitted category	
586 to 1 000			−0.00	−0.01
1 001 to 1 500			0.22	1.63
> 1 500 hrs			1.05	2.61 **
Number of driver-years	4 099		4 099	
Number of variables	49		55	
Log-Likelihood	−1 085.66		−1 074.80	
Log-Likelihood Ratio Test	$\chi^2_{20} = 34.74$** Model 5 vs Model 3		$\chi^2_6 = 21.72$** Model 6 vs Model 5	
	$\chi^2_8 = 38.70$** Model 5 vs Model 4		$\chi^2_{32} = 98.94$** Model 6 vs Model 1	

*Significant at 10%.
**Significant at 5%.

Gresset J, Meyer F. Risk of automobile crashes among elderly drivers with impairments or chronic diseases. Canadian Journal of Public Health 1994; 85: 282-285														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
	✓													
Research Question	To evaluate the influence of medical conditions, including heart disease, on crash risk among 70 year olds													
Study Design	Case control													
Population	**Inclusion Criteria**	Males registered to drive a passenger vehicle in Quebec; aged 70 years in 1988 or 1989; in crashes that yielded mild bodily injury. Controls were randomly selected from 30,000+ male drivers who did not have a crash while 70 years old during 1988-1989. Controls were matched based upon area of residence.												
	Exclusion Criteria	Drivers involved in crashes yielding fatalities or bodily damage leading to hospitalization.												
	Study population characteristics	Variable	Values											
		n	1,400 cases and 2,636 controls											
		Age: (yrs.) mean ±SD	70 years											
		Height (cm) mean ±SD	Not reported											
		Weight (kg) mean ±SD	Not reported											
		Gender M/F	100% M											
	Generalizability to CMV drivers	Unclear. This studied population may be more aged than most commercial drivers and drive fewer miles. This population consists of non-commercial drivers. Data from crashes with severe injury or fatality were excluded.												
Methods	Drivers were matched with controls. Crash rates were then compared.													
Statistical Methods	Odds ratios (ORs) were calculated, using multiple logistic regression to control for time per week spent driving, time per week spent driving during rush hour, and mileage													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
	Score = 7.7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes during drivers' 70th year													
Results	Percent of chronic impairments and diseases among the study population is listed in Table G-20. Among drivers with any type of heart disease, the relative risk of crashes was close to one, with a tight confidence interval (OR =1.04, CI-0.91-1.20). Thus, overall, patients with heart diseases did not have an increased risk of crashes while driving. The risks of road crashes among drivers with hypertension and heart failure were very similar to those among drivers who did not suffer from these diseases. However, for subjects affected by arrhythmias, a statistically significant increase in the risk of crashes was observed (OR=1.63, 95% CI 1.00-2.65). Drivers with ischemic heart disease had a moderate increase in the risk of crashes that was not statistically significant (OR=1.13; CI 0.96 – 1.34). Increased time driving													

	(>9 hours per week) and increased distance of driving were associated with higher rates of crashes (Table G-21).
Authors' Comments	Overall, results suggest that drivers of private vehicles with impairments or chronic medical conditions are not at increased risk of road crashes. Only drivers with arrhythmias had a statistically significant increase in risk.

Table G-20. Prevalence of Chronic Impairments and Diseases among 1,400 Cases and 2,636 Controls

	Cases		Controls	
	N	%	N	%
Visual impairments	118	8.4	209	7.9
- Minimal VA	52	3.7	99	3.8
- Monocularity	5	0.4	10	0.4
- Minimal VA monocularity	61	4.4	100	3.5
Other impairments	120	8.6	228	8.7
- Hearing impairments	57	4.1	119	4.5
- Amputations	13	0.9	29	1.1
- Paralyses	50	3.6	80	3.0
Heart diseases	448	32.0	820	31.1
- Hypertension	176	12.6	346	13.1
- Heart failure	18	1.3	36	1.4
- Arrhythmias	30	2.1	35	1.3
- Ischemic heart disease	260	18.6	442	16.8
Diabetes mellitus	121	8.6	226	8.6
- Non-insulin-dependent	103	7.4	196	7.4
- Insulin-dependent	18	1.3	30	1.1

Table G-21. Odds Ratios of Crashes and Related 95% Confidence Intervals for Chronic Impairments And Diseases Among 70-year-old Drivers

	Odds Ratio	95% Confidence Interval	
Visual impairments	1.07	0.84	1.36
- Minimal VA	0.99	0.71	1.40
- Monocularity	0.95	0.32	2.77
- Minimal VA monocularity	1.16	0.83	1.60
Other impairments	0.99	0.78	1.26
- Hearing impairments	0.90	0.65	1.24
- Amputations	0.84	0.44	1.67
- Paralyses	1.18	0.89	1.70
Heart diseases	1.04	0.91	1.20
- Hypertension	0.95	0.78	1.16
- Heart failure	0.94	0.53	1.66
- Arrhythmias	1.63	1.00	2.65
- Ischemic heart disease	1.13	0.96	1.34
Diabetes mellitus	1.01	0.80	1.27
- Non-insulin-dependent	0.99	0.77	1.27
- Insulin-dependent	1.13	0.63	2.04

<table>
<tr><td colspan="15">Guibert R, Potvin L, Ciampi A, Loiselle J, Philibert L, Franco E. Are drivers with CVD more at risk for motor vehicle crashes? Study of men aged 45 to 70. Can Fam Physician 1998; 44:770-776</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine whether male drivers aged 45-70 years suffering from cardiovascular disease (CVD) are more likely to be involved in motor vehicle crashes (MVC) that are reported to the police</td></tr>
<tr><td>Study Design</td><td colspan="14">Population-based case-control</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Francophone male drivers aged 45-70 involved in passenger car motor vehicle collisions in Quebec during a 6-month period who responded to a questionnaire</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Drivers of commercial vehicles</td></tr>
<tr><td>Study population characteristics</td><td colspan="13"><u>Variable</u> — <u>Values</u>
n — 5,024: 2,504 in crashes, 2,520 controls
Age: (yrs.) mean ±SD — Range 45 - 70 yrs
Height (cm) mean ±SD — NR
Weight (kg) mean ±SD — NR
Gender M/F — 100% M</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear. No commercial drivers were included in sample. Drivers from Quebec only.</td></tr>
<tr><td>Methods</td><td colspan="14">Individuals in study were randomly selected by computer and sent a questionnaire by mail. The questionnaire queried about mileage, willingness to drive in inclement weather, sociodemographic characteristics, and other items in addition to questions about medical condition.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Pearson's correlation coefficient (likelihood ratio), X^2, t-test. Independent variables were examined for collinear points. Crude and adjusted Ors and 95% confidence intervals (CI) were estimated through multivariate stepwise hierarchal logistic regressions for risk of MVCs and following the conceptual model. Covariates were included at the 0.10 level of significance and excluded at the 0.20 level</td></tr>
<tr><td rowspan="6">Quality Assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Score = 7.7</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Moderate</td><td>27</td><td>28</td><td colspan="11"></td></tr>
<tr><td></td><td></td><td colspan="11"></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Crashes per time</td></tr>
<tr><td>Results</td><td colspan="14">Analysis of the SAAQ files' entire sample of 5,024 drivers showed that drivers suffering from CVD were less likely to be involved in MVCs (odds ratio [OR] 0.82, 95% confidence interval [CI] 0.67 to 0.99) than drivers without CVD. Although the estimate of risk remains unchanged when adjusted for age, it becomes statistically insignificant. It also remains unchanged and statistically insignificant when adjusted for yearly distance driven and driver behavior, as shown by responses to other questionnaire. Drivers suffering from CVD drove significantly less each year (8900 km) than drivers without medical</td></tr>
</table>

	conditions (13000 km) (Table G-22 and Table G-23).
Authors' Comments	This study shows no increased risk of motor vehicle crashes for drivers suffering from CVD.

Table G-22. Distribution of Cardiovascular Diseases by Age Group

MEDICAL CONDITION	45-54 YEARS N=1731 (%)	55-64 YEARS N=1713 (%)	65-70 YEARS N=1580 (%)	ALL AGES N=5024 (%)
CVD	71 (4.1)	139 (8.1)	232 (14.7)	442 (8.8)
CHD Only	36 (2.1)	71 (4.1)	141 (8.9)	248 (4.9)
CHD functional severity				
I	28 (1.6)	62 (3.6)	107 (6.8)	197 (3.9)
II	5 (0.3)	7 (0.4)	30 (1.9)	42 (0.8)
III	3 (0.2)	2 (0.1)	4 (0.3)	9 (0.2)

Table G-23. Risk of Involvement in Motor Vehicle Crashes for Those Reporting Cardiovascular Disease (N=5,024)

VARIABLES	NUMBER INVOLVED IN MVCS	NUMBER NOT INVOLVED IN MVCS	OR (95% CI)
In the SAAQ database			
• Crude odds	2504	2520	0.82 (0.67-0.99)
• Controlled for age	2504	2520	0.82 (0.67-1.00)
Questionnaire respondents			
• Crude odds	784	987	0.85 (0.62-1.17)
• Controlled for age	784	987	0.86 (0.63-1.18)
• Additional confounding variable*	784	987	0.86 (0.63-1.19)
• Additional covariate†	458	633	0.70 (0.45-1.10)

*The confounding variable controlled for was alcohol consumption.

†The only covariate in the final model was marital status (at the .10 level).

Jovanovic J, Batanjac J, Jovanovic M. The influence of cardiovascular diseases of the drivers on the occurrence of traffic crashes. Vojnosanit Pregl 1999; 56(1): 3-8														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
	✓													
Research Question	To establish the prevalence and influence of cardiovascular disorders on the occurrence of traffic crashes													
Study Design	Prospective cohort													
Population	**Inclusion Criteria**	Individuals with cardiovascular disease												
	Exclusion Criteria	Not reported												
	Study population characteristics	Variable n Age: (yrs.) mean ±SD Height (cm) mean ±SD Weight (kg) mean ±SD Gender M/F					Values 620 drivers with cardiovascular disease, and 280 healthy drivers 51.8 (12.3) among drivers with cardiovascular disease, 52.1 (11.9) among healthy drivers Not reported Not reported 69.2% of cases M; 70.7% of controls M							
	Generalizability to CMV drivers	Unclear. Mostly male population.												
Methods	Numbers of crashes caused by enrolled individuals were collected for five years. This data were compared.													
Statistical Methods	T-test and X^2													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	N	N	Y	N	N	N	N	Y	N	Y	Y	Y
	Score = 4.6	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Low	**27**	**28**											
Relevant Outcomes Assessed	Number of crashes													
Results	139 (22.4%) drivers from the test group had traffic crashes, which were significantly more, compared to the control group (10.3% P <0.01). The average number of traffic crashes per driver in the test group was 2.4 ± 0.8 and in the control group 0.8 ± 0.1 (p <0.001) (Table G-24 - Table G-26.).													
Authors' Comments	We have observed that the drivers from the test group had caused traffic crashes more frequently and on average had significantly higher number of traffic crashes compared to the drivers in the control group. Arterial hypertension and arrhythmia were significantly more frequent in professional drivers.													

Table G-24. Number of Drivers Who Had Traffic Crashes

	n	n with Crashes	%
Control Group	280	29	10.3
Test Group	620	139	22.4**
Arterial hypertension	328	92	28.1***
Coronary artery disease	68	10	14.7
Thromboangiitis obliterans	48	17	35.4*
Arrhythmia	176	20	11.4

*p <0.05; **p <0.01; ***p <0.001, compared to control

Table G-25. Average Number of Traffic Crashes for Drivers with and Without Cardiovascular Disease

	With cardiovascular disease	Without cardiovascular disease	SD
Control Group	280	0.8	0.1
Test Group	620	2.4***	0.8
Arterial hypertension	328	2.9***	0.7
Coronary artery disease	68	2.8***	0.8
Thromboangiitis obliterans	48	3.1***	1.2
Arrhythmia	166	1.1***	0.05

***p<0.001, compared to control

Table G-26. Number of Drivers Who Had Traffic Crashes by Duration and Type of Cardiovascular Disease

Duration of the disease (years)	Arterial hypertension			Coronary Disease			Thromboangiitis obliterans			Arrhythmia		
	n	n1	%	n	n1	%	n	n1	%	n	n1	%
0-5	28	1	3.6	10	0	0.0	0	0	0.0	37	1	2.7
6-10	36	4	11.1	12	1	8.3	3	0	0.0	30	1	3.3
11-15	85	20	23.5	13	3	23.1	16	4	25.0	38	4	10.5
16-20	91	28	30.8	15	2	13.3	14	6	42.8	36	8	22.2
>20	88	39	44.3	18	4	22.2	15	7	46.7	35	6	17.1
Total	328	92	28.1	68	10	14.7	48	17	35.4	176	20	11.4

n = total number; n1 = number with crashes

<table>
<tr><td colspan="15">Koepsell T, Wolf M, McCloskey L, Buchner D, Louie D, Wagner E, Thompson R. Medical conditions and motor vehicle collision injuries in older adults. JAGS 1994; 42(7): 695-700</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">To determine whether medical conditions that can impair sensory, cognitive, or motor function increase the risk of injury due to motor vehicle collision in older drivers</td></tr>
<tr><td>Study Design</td><td colspan="14">Retrospective case-control</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Licensed drivers at least 65 years old and members of the Group Health Cooperative (GHC) Health Maintenance Organization treated at GHC's facilities in Washington State. Cases had sustained injuries in a motor vehicle collision while driving and were treated within 7 days between 1987 and 1988, as identified by medical records or claims review, and relevant police reports were obtained. Controls were selected randomly from GHC enrollees who had not been injured while driving in a collision within one calendar year of the reference date (usually date of collision) of cases. Two controls were matched to each case based upon age (within 1 year), gender, and country of residence.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="13"><u>Variable</u> — <u>Values</u>
n — 680 (234 cases; 446 controls)
Age: (yrs.) mean ±SD — 65+ yrs
Height (cm) mean ±SD — Not reported
Weight (kg) mean ±SD — Not reported
Gender M/F — 340/340</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear. Drivers were from Washington State only.</td></tr>
<tr><td>Methods</td><td colspan="14">Diagnoses made within 3 years of the reference (crash) date, including electrocardiogram abnormalities, were obtained by review of patients' medical records. Information about driving habits, miles driven per year, "health habits," and sociodemographic characteristics were obtained by mailed or telephone survey.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Odds ratios were used to estimate relative risk. Analyses that controlled only for the matching factors (age, gender, and county) were based on Mantel-Haenszel techniques for stratified data, with each matched set forming its own small stratum. Analyses that controlled for additional potential confounding factors were carried out with conditional logistic regression.</td></tr>
<tr><td rowspan="6">Quality Assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Score = 8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
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<tr><td rowspan="2">Category= Moderate</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Myocardial infarction, angina pectoris, coronary artery bypass, survival of cardiac arrest, injury among persons with one or more EKG abnormalities, prevalence of hypertension, relation of other medical conditions to motor vehicle collision (fall in previous year), depression, alcohol abuse, chronic</td></tr>
</table>

	obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, cancer, diabetes mellitus
Results	About 21% of cases and 16% of controls had a history of coronary heart disease (Odds ratio 1.4 95% CI 1.0 – 2.2). The odds ratios for myocardial infarction, angina pectoris, and coronary artery bypass grafting were similar, but with wider confidence limits that included 1.0. Several cardiac arrhythmias and conduction system abnormalities were more common among cases than among controls (atrial fibrillation was the sole exception), but confidence limits for the odds ratios were quite wide and included 1.0 in all instances. More cases than controls had a pacemaker at reference date, but again, the rarity of pacemaker use yielded very wide confidence limits around an estimated odds ratio of 6.5. Overall, the findings suggest that the relative risk among persons with 1 or more of the various EKG abnormalities was about 1.3 (95% CI 0.9 – 1.8). There was little difference between cases and controls with respect to the prevalence of hypertension (Table G-27).
Authors' Comments	We found modest elevations in risk for persons with various arrhythmias and conduction system abnormalities on the resting electrocardiogram that could transiently interfere with cerebral perfusion. These associations, however, were neither individually nor collectively strong enough to achieve statistical significance. Thus, while associations between cardiac abnormalities and driving risk remain clinically plausible, this study suggests that the excess risk among older drivers with these conditions is not large.

Table G-27. Relative risk of motor vehicle collision injury in relation to selected cardiovascular conditions

Condition	Percent Prevalence among		Odds Ratio	
	Cases (*n* = 234)	Controls (*n* = 446)	Est.	(95% CI)
Coronary heart disease				
• Myocardial infarction	7.3	6.1	1.2	(0.6-2.3)
• Angina pectoris	19.7	14.1	1.5	(0.9-2.2)
• Coronary-artery bypass graft	2.6	1.6	1.6	(0.6-5.0)
• Primary cardiac arrest	0.0	0.2	0.0	
• Any of above forms of coronary heart disease	21.4	15.5	1.4	(1.0-2.2)
EKG abnormalities				
• Arrhythmias				
o Atrial fibrillation	5.6	6.3	0.9	(0.4-1.7)
o Paroxysmal supraventricular tachycardia	3.4	2.7	1.3	(0.5-3.2)
o Premature ventricular contractions	8.5	5.6	1.6	(0.8-2.9)
o Sinus bradycardia	14.6	12.6	1.4	(0.9-2.2)
o Any of above arrhythmias	23.5	24.7	1.2	(0.8-1.7)
• Conduction-system abnormalities				
o First-degree AV block	5.1	3.1	1.8	(0.8-4.0)
o Second- or third-degree AV block	0.4	0.2	2.0	(0.1-32.0)
o Left bundle branch block	1.3	1.1	1.1	(0.3-4.5)
o Right bundle branch block	2.6	1.6	1.6	(0.6-5.0)
o Left anterior hemiblock	2.6	1.4	2.0	(0.7-6.2)
o Any of above conduction-system abnormalities	9.5	6.9	1.6	(0.9-2.8)
• Any of above EKG abnormalities	27.9	28.9	1.3	(0.9-1.8)
Pacemaker	1.7	0.4	6.5	(0.7-64.6)
Hypertension	33.3	37.0	0.8	(0.6-1.2)

McGwin G, Sims R, Pulley, L, Roseman J. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: A population-based case-control study. American Journal of Epidemiology 2000; 152:424-431														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
	✓													
Research Question	To identify medical conditions and medications associated with risk of at-fault crashes among older drivers													
Study Design	Population-based case control													
Population	**Inclusion Criteria**	Drivers aged 65+ involved in a crash (cases) in 1996 in Mobile County, Alabama. Controls were matched for not having a crash during the same year. All included individuals were selected from Alabama Department of Public Safety driving records.												
	Exclusion Criteria	Potential controls that had stopped driving prior to 1996. Those who refused or were unable to participate in the telephone survey were excluded.												
	Study population characteristics	Variable n Age: (yrs.) mean ±SD Height (cm) mean ±SD Weight (kg) mean ±SD Gender M/F	Values 901 (244 cases at-fault cases, 182 not-at-fault cases, and 475 controls) Mean age not reported, all included were 65+ Not reported Not reported 49.6% of at-fault drivers in crashes M, 51.1% of drivers not at fault for crashes M Gender of controls not reported												
	Generalizability to CMV drivers	Unclear												
Methods	Cases and controls were identified through police and safety records. A random sample was selected. Most were called for a telephone interview. Those who participated (74.1% of eligible controls) answered questions about chronic medical conditions, driving habits, visual function, and were assessed for cognitive status.													
Statistical Methods	Odds ratios													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y
	Score = 7.7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes over time													
Results	Older drivers with heart disease (odds ratio (OR) =1.5, 95% confidence interval (CI): 1.0, 2.2) or stroke (OR=1.9, 95% CI 0.9, 3.9) were more likely to be involved in at-fault automobile crashes (Table G-28).													

Authors' Comments	Older drivers with heart disease or stroke were more likely to be involved in both at-fault and not-at-fault automobile crashes. These associations, however, appear to be independent of the medications used to treat these diseases.

Table G-28 Medical Characteristics of At-Fault Drivers Involved in Crashes, Not-at-Fault Drivers Involved in Crashes, and Drivers not Involved in Crashes from Mobile County Alabama, January to December 1997

	% at-fault drivers involved in crashes (n = 249)	Drivers not involved in crashes (n = 454)					Not-at-fault drivers involved in crashes (n = 198)				
		%	OR*,†	95% CI*	OR‡	95% CI	%	OR†	95% CI	OR†,‡	95% CI
High blood pressure	42.9	45.7	0.9	0.6, 1.2	0.9	0.6, 1.3	45.7	0.9	0.6, 1.3	0.9	0.6, 1.4
Heart disease	26.0	20.2	1.4	0.9, 2.0	1.5	1.0, 2.2	24.3	1.1	0.7, 1.7	1.0	0.7, 1.7
Stroke	7.3	4.1	1.8	0.9, 3.7	1.9	1.0, 3.9	6.9	1.1	0.5, 2.3	1.1	0.5, 2.4
Cancer	15.3	13.7	1.1	0.7, 1.8	1.2	0.7, 1.9	13.9	1.1	0.6, 2.0	1.0	0.5, 1.8
Arthritis	48.6	43.3	1.2	0.9, 1.7	1.2	0.9, 1.7	47.4	1.1	0.7, 1.6	1.0	0.7, 1.5
Cataracts	44.6	42.8	1.1	0.8, 1.5	1.0	0.7, 1.5	35.1	1.5	1.0, 2.2	1.1	0.7, 1.8
Glaucoma	6.9	8.9	0.8	0.4, 1.4	0.7	0.4, 1.3	5.2	1.4	0.6, 3.2	1.0	0.4, 2.5
Diabetes	13.6	14.0	1.0	0.6, 1.5	0.9	0.6, 1.5	16.0	0.8	0.5, 1.4	0.9	0.5, 1.5
Kidney disease	3.2	4.7	0.7	0.3, 1.6	0.7	0.3, 1.6	6.4	0.5	0.2, 1.2	0.4	0.2, 1.2
Diabetic retinopathy	1.6	1.5	1.1	0.3, 3.8	1.4	0.3, 4.0	1.1	1.5	0.3, 8.2	1.9	0.3, 10.9
Diabetic neuropathy	1.2	0.6	2.0	0.4, 9.8	2.6	0.5, 13.1	0.5	2.3	0.2, 21.8	2.8	0.3, 28.3
Near vision score ≤ 75%§	13.2	12.3	1.1	0.7, 2.0	1.0	0.6, 1.7	8.0	1.8	0.9, 3.4	1.6	0.8, 3.3
Far vision score ≤ 75%§	41.0	36.5	1.2	0.9, 1.7	1.2	0.8, 1.7	36.0	1.2	0.8, 1.9	1.1	0.7, 1.7
Peripheral vision score ≤ 75%§	8.5	6.0	1.5	0.8, 2.7	1.4	0.8, 3.0	4.7	1.9	0.8, 4.5	1.6	0.7, 3.9
Cognitive impairment¶	12.8	13.8	0.9	0.6, 1.5	0.8	0.5, 1.4	10.0	1.3	0.7, 2.6	1.1	0.7, 2.6

* OR, odds ratio; CI, confidence interval.
† Reference is those without condition.
‡ Adjusted for age, gender, race, and annual mileage.
§ Lower scores represent greater impairment.
¶ Three or more errors on the Short Portable Mental Status Questionnaire.

<table>
<tr><td colspan="15">Medgyesi M, Koch D. Medical impairments to driving: cardiovascular disease. 39th annual proceedings of the Association for the Advancement of Automotive Medicine, October 16-18, 1995, Chicago, IL; 483-499</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">To assess whether cardiovascular disease (CVD) is a medical impairment to driving</td></tr>
<tr><td>Study Design</td><td colspan="14">Retrospective case control</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Drivers with cardiovascular disease in the Saskatchewan Government Insurance (SGI) database were identified by physicians or by hospital use either enrolled in the SGI program or not. Controls were identified from other SGI studies. Controls were matched based upon age (closest category possible), gender, population of place of residence, license class, and period of driving (time spent in the SGI program), and co-morbid conditions. Data was collected between 1/1/1980 and 12/31/1989.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="13"><u>Variable</u> — <u>Values</u>
n — 29,007 drivers with CVD, number of control drivers unclear
Age: (yrs.) mean ±SD — Not reported
Height (cm) mean ±SD — Not reported
Weight (kg) mean ±SD — Not reported
Gender M/F — Not reported</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear. Some drivers in this sample are commercial drivers. All drivers were Canadian.</td></tr>
<tr><td>Methods</td><td colspan="14">Drivers were identified from an SGI database of all drivers, including commercial drivers, in SGI's medical review program. Police-reported collisions between 1/1/1980 and 12/31/1989 were obtained from files of the Saskatchewan Highway and Transportation. Data on medical conditions was obtained from the Saskatchewan Health Plan database and the Medical Care Insurance Branch database. Program drivers were those with cardiovascular disease identified by the SGI's medical review program. Non-program drivers were those identified as having cardiovascular disease by health plan and medical insurance data bases, but not identified by the SGI's medical review program. Drivers were stratified according to age, gender, place of residence, and license class. Non-program (with CVD identified by SGI's medical review program) and control drivers were matched to program drivers. Crash rates were then compared.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Categorical regression (e.g., McCullagh and Nelder 1989) and the SAS CATMOD procedure were used to assess separate generalized linear models of the natural logarithm of the collision rates per licensed driver in a manner analogous to Zador (1991). In this procedure, a significant factor effect indicates that, controlling for all other factors in the model, the distribution of crash rates differs across factor levels. ANOVAs were performed.</td></tr>
<tr><td rowspan="6">Quality Assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Score = 7.7</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
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<tr><td>Category=</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

	Moderate													
Relevant Outcomes Assessed	Crashes over time													
Results	Non-program and program drivers diagnosed with cardiovascular disease consistently performed worse than control drivers in "at fault" crashes in which the driver's condition or action was considered to be a major contributing factor (Table G-29).													
Authors' Comments	Subjects were classified by license class to allow for an assessment of the differences in crash risk between commercial (class 1, 2, 3, and 4) and non-commercial (class 5) drivers. Evidence of higher crash rates among commercial drivers with cardiovascular disease relative to non-commercial drivers with the condition, would suggest that commercial drivers with the condition pose a greater traffic safety risk than their non-commercial counterparts. The results of the study suggest that poor driving performance was associated with the presence of cardiovascular disease. However, there was no evidence to suggest these results differed by license class.													

Table G-29. Driver Involvements per 1,000 Licensed Drivers by Medical Review Status, Pre/Post Program Enrollment, and Fault

Pre-period

Medical review status	*Drivers*	*At-fault*	*Not-at-fault*	*Relative risk*
Control	1462	33	51	0.65
Non-program	1462	55	56	0.98
Program	731	211	77	2.75

Post-period

Medical review status	*Drivers*	*At-fault*	*Not-at-fault*	*Relative risk*
Control	1462	37	47	0.79
Non-program	1462	45	44	1.03
Program	731	98	71	1.38

Percent change from pre- to post-period

Medical review status	*At-fault*	*Not-at-fault*	*Relative risk*
Control	12.5	-8.1	22.4
Non-program	-17.5	-22.0	5.7
Program	-53.2	-7.1	-49.7

Naughton T, Pepler R, Waller J. Investigate road crash risk levels for heart attack (myocardial infarction) victims. NTIS, DOT HS-806-383; 1982: 1-31														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
	✓													
Research Question	To examine whether drivers with ischemic heart disease (IHD) have an increased crash risk compared to age-gender-residence (AGR) matched controls. The role of risk exposure (e.g., miles driven, type of traffic) was also investigated.													
Study Design	Retrospective case control													
Population	**Inclusion Criteria**	Patients admitted for IHD at one of two hospitals (Medical Center Hospital of Vermont and Fanny Allen Hospital) in Burlington VT, and discharged between January 1, 1975 and December 31, 1979.												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable	Values											
		n	725 cases, 241 controls											
		Age: (yrs.) mean ±SD	Not reported											
		Weight (kg) mean ±SD	Not reported											
		Gender M/F	76% M											
	Generalizability to CMV drivers	Unclear. Sample is predominantly male.												
Methods	The crash risk of each patient with IHD was compared to two matched controls, an AGR control, and a gender-residence (GR) match, who had not been hospitalized for IHD over the sample period. DMV records were examined from January 1975 - June 1981 for crash data.													
Statistical Methods	Chi-square test of frequency distribution of crashes between patient and each comparison group													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y
	Score = 7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crash frequency over time													
Results	204 (28.1%) of cases crashed, compared to 236 AGR matched comparisons (33.6%) and 248 GR match comparisons (34.2%). Chi-square test showed no significant difference between patients and AGR controls, but a statistically significant difference between patients and GR matched group. The overall crash rate for IHD patients was 4.8 % per year compared to 6.8 % and 8.2 % for AGR and GR comparison groups, respectively (Table G-30). Crash rates were still lower when corrected for an estimated 20% reduction in mileage for the patient group. (This estimate for reduced mileage was from an independent AARP study)													
Authors' Comments	Patients with CVD-IHD were not found to crash more frequently, perhaps because IHD patients reduce their driving risks (e.g., they drive less, or during less busy times).													

Table G-30. Crash Rates per Year for Patients: Age/Gender /Residence and Gender/Residence Comparison Groups

Crash Data		PT	(x 1.20*)	AGR	GR
Overall		.048	(.058)	.068	.082
	M	.058	(.070)	.075	.085
	F	.020	(.024)	.068	.073
Single Vehicle		.005	(.006)	.008	.013
	M	.005	(.006)	.009	.016
	F	.005	(.006)	.005	.025
PDO		.037	(.044)	.055	.062
	M	.044	(.053)	.060	.064
	F	.015	(.018)	.037	.059
Injury		.011	(.013)	.014	.019
	M	.013	(.026)	.015	.021
	F	.006	(.007)	.011	.015

* Patient rate adjusted for average 20% reduction in mileage.

Vernon D, Diller E, Cook L, Reading J, Suruda A, Dean J. Evaluating the crash and citation rates of Utah drivers licensed with medical conditions, 1992-1996. Accid Anal Prev 2002; 34(2): 237-46													
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**								
	✓												
Research Question	Rates of adverse driving events (crash, at-fault crash, and citations) experienced by drivers licensed with medical conditions												
Study Design	Retrospective case-control												
Population	**Inclusion Criteria**	All Utah-licensed drivers with a medical condition on their licenses 1992-1996											
	Exclusion Criteria	None reported											
	Study population characteristics	Variable	Values										
		n	19,039 drivers with CVD, 109,540 controls										
		Age: (yrs.) mean ±SD	55.8 (19.4) cases, 37.0 (17.5) controls										
		Weight (kg) mean ±SD	Not reported										
		Gender M/F	Not reported										
	Generalizability to CMV drivers	Unclear, This sample included all drivers with medically restricted licenses.											
Methods	All drivers' license data were obtained from the Utah Driver License division. Death certificate data was obtained from Utah Resource for Genetic and Epidemiological Research and Utah Department of Health database. Data on crashes (police reports) were obtained from the Utah Department of Transportation. Databases were linked with probabilistic linkage methodology. Rates of adverse driving events were then compared between cases and controls over 5-year period per 10,000 days. Controls were selected based on age, gender, and place of residence.												
Statistical Methods	Relative risks were calculated based upon X^2 distribution												
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		S	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y
	Score = 7.8	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes, at-fault crashes, traffic violations													
Results Q1	Drivers with restrictions due to cardiovascular disease did not differ from controls on crash rate or at-fault crash rate, and had lower traffic violation rates than controls (Table G-31, Table G-32, and Table G-33).													
Authors' Comments	Drivers in Utah medical conditions program had modestly elevated rates of adverse driving events compared to matched controls. Possible underreporting of medical conditions and accurate assessment of exposure rates are potential weaknesses in this study.													

Table G-31. Relative Risk for Adverse Driving Events of Drivers Reporting Single Medical Conditions, Compared to Controls

	Restriction status	Rate per 10,000 license days		RR[a]	LCL[b]	UCL[c]
		Medical Conditions	Controls			
Citation	Not restricted	2.50	2.29	1.09	1.07	1.12*
	Restricted	2.29	2.41	0.95	0.84	1.07
	Excluded	2.45	3.26	0.75	0.50	1.10
Crash	Not restricted	1.65	1.23	1.33	1.30	1.37*
	Restricted	1.67	1.32	1.26	1.08	1.44*
	Excluded	1.14	1.46	0.78	0.44	1.37
At-fault crash	Not restricted	0.99	0.66	1.49	1.44	1.55*
	Restricted	1.39	0.80	1.74	1.49	2.04*
	Excluded	1.05	0.82	1.29	0.71	2.34

[a] RR: relative risk; [b] LCL: 95% lower confidence limit; [c] UCL: 95% upper confidence limit

* Significantly different from control, $P < 0.05$ (confidence interval does not include 1.0).

Table G-32. Relative Risk for All Crashes, Drivers Reporting Single Medical Condition vs Control Drivers (Utah 1992-1996)

	Restriction status	Rate per 10,000 license days		RR[a]	LCL[b]	UCL[c]
		Medical Conditions	Controls			
Diabetes	Not restricted	1.70	1.30	1.30	1.23	1.38*
	Restricted	2.03	1.47	1.38	0.75	2.54
Cardiovascular	Not restricted	1.04	1.05	0.99	0.93	1.06
	Restricted	1.35	0.98	1.37	0.43	4.38
Pulmonary	Not restricted	1.52	1.29	1.18	1.03	1.34*
	Restricted	1.04	1.14	0.91	0.40	2.09
Neurological	Not restricted	1.90	1.17	1.62	1.32	1.99*
	Restricted	1.75	1.31	1.33	0.78	2.28
Epilepsy	Not restricted	2.69	1.55	1.73	1.58	1.90*
	Restricted	2.67	1.81	1.47	1.06	2.03*
Learning, memory	Not restricted	3.31	1.51	2.19	1.33	3.61*
	Restricted	5.14	0.00			
Psychiatric	Not restricted	2.24	1.43	1.57	1.46	1.67*
	Restricted	2.57	1.37	1.87	1.11	3.17*
Alcohol and drugs	Not restricted	3.09	1.70	1.82	1.18	2.81*
	Restricted	9.99	2.37	4.21	1.80	9.85*
Visual acuity	Not restricted	1.75	1.30	1.35	1.25	1.46*
	Restricted	1.40	1.10	1.27	1.04	1.55*
Musculoskeletal	Not restricted	1.64	1.03	1.59	1.10	2.29*
	Restricted	2.22	0.49	4.51	1.01	20.12*

Functional motor	Not restricted	1.56	1.41	1.11	0.70	1.74
	Restricted	0.00	1.69		`	

[a] RR: relative risk; [b] LCL: 95% lower confidence limit; [c] UCL: 95% upper confidence limit

* Significantly different from control, $P < 0.05$ (confidence interval does not include 1.0).

Table G-33. Relative Risk for At-Fault Crashes by Drivers Reporting Single Medical Condition vs Controls (Utah 1992-1996)

	Restriction status	Rate per 10,000 license days		RR[a]	LCL[b]	UCL[c]
		Medical Conditions	Controls			
Diabetes	Not restricted	1.02	0.70	1.46	1.36	1.58*
	Restricted	1.48	0.83	1.77	0.87	3.61
Cardiovascular	Not restricted	0.55	0.55	1.00	0.92	1.09
	Restricted	0.90	0.58	1.54	0.37	6.40
Pulmonary	Not restricted	0.85	0.68	1.26	1.06	1.50*
	Restricted	1.04	0.65	1.60	0.69	3.71
Neurological	Not restricted	1.32	0.60	2.20	1.71	2.84*
	Restricted	1.09	0.78	1.40	0.71	2.76
Epilepsy	Not restricted	1.76	0.87	2.02	1.80	2.27*
	Restricted	2.40	1.00	2.39	1.70	3.36*
Learning, memory	Not restricted	2.56	0.77	3.32	1.84	5.99*
	Restricted	5.14	0.00			
Psychiatric	Not restricted	1.37	0.75	1.85	1.69	2.01*
	Restricted	2.22	0.77	2.89	1.64	5.07*
Alcohol and drugs	Not restricted	1.83	0.82	2.22	1.25	3.94*
	Restricted	8.33	1.45	5.75	2.26	14.61*
Visual acuity	Not restricted	1.15	0.75	1.52	1.38	1.68*
	Restricted	1.17	0.75	1.56	1.25	1.94*
Musculoskeletal	Not restricted	0.98	0.53	1.84	1.14	2.98*
	Restricted	2.22	0.20	11.29	2.39	53.25*
Functional motor	Not restricted	1.22	0.71	1.71	1.00	2.93
	Restricted	0.00	1.21			

[a] RR: relative risk; [b] LCL: 95% lower confidence limit; [c] UCL: 95% upper confidence limit

* Significantly different from control, $P < 0.05$ (confidence interval does not include 1.0).

Waller, J. Cardiovascular disease, aging, and traffic crashes. J Chron Dis 1967; 20:615-620														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
	✓													
Research Question	To compare crash risk among drivers ages 30-59, and healthy and impaired persons age 60 and older													
Study Design	Survey and driving record review													
Population	**Inclusion Criteria**	Persons with drivers licenses that fell into one of the following groups: (1) age 60+ with healthy cardiovascular (inc. blood pressure, EKG, lack of symptoms) and no signs of senility (i.e., fainting, dizziness or cognitive symptoms); (2) age 60+ with healthy cardiovascular tests but episodes of senility; (3) age 60+ with cardiovascular changes, but no senility; (4) age 60+ with cardiovascular disease and senility; (5) consecutive drivers aged 30-59 from the same community who were renewing their drivers licenses												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable	Values											
		n	444											
		Age: (yrs.) mean ±SD	By group: (1) 68; (2) 70; (3) 70; (4) 72; (5) 46; Mean of sample groups 70.5 years. No measure of variance reported.											
		Weight (kg) mean ±SD	Not reported											
		Gender M/F	47% M											
	Generalizability to CMV drivers	Unclear												
Methods	Persons 60+ in a specific community were evaluated medically and by survey for cardiovascular changes and signs of senility. Information on traffic violations and crashes was obtained from the Department of Motor Vehicles (DMV). Crash rates per million and violation rates per 100,000 miles were calculated for all individuals.													
Statistical Methods	T-test													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
	Score = 7.7	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes, violations													
Results	Drivers with cardiovascular changes appeared to have excessive crash and violation rates when compared with younger, presumably healthier drivers. Differences however were not significant (Table G-34).													
Authors'	Drivers with cardiovascular disease had an apparent increase in crash and violation rates, but the													

Comments	differences were not statistically significant.

Table G-34. Average Individual Crash and Violation Rates by Medical Category for Residents of Seal Beach, CA

Medical category	3-yr Driving exposure in million miles	Crashes/ 1,000,000 miles	Violations/ 100,000 miles
"Healthy", age 30-59	7.1	9.1	3.0
"Healthy", age 60 or older	1.5	12.1	3.3
Senile, age 60 or older	1.2	19.3*	3.3
Cardiovascular changes, age 60 or older	1.2	14.7	4.6
Cardiovascular changes and senility, age 60 or older	2.7	36.2*	5.8†

* P<0.03 between senile drivers and those age 30-59; P=0.005 between drivers with cardiovascular changes and senility and those age 30-59.
† P<0.02 when compared with drivers age 30-59.

Waller, JH. Chronic medical conditions and traffic safety: review of the California experience. NEJM 1965; 273:1413-1420														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
	✓													
Research Question	To investigate whether drivers with known medical conditions (include cardiovascular disease) have higher traffic crash and violation rates than drivers not known to have these medical conditions													
Study Design	Population case-control													
Population	**Inclusion Criteria**	Cases were consecutive persons with known medical conditions who were under review (including change of address, routine medical reporting) with the California Department of Motor Vehicles. Controls were randomly selected drivers who had applied for license renewal.												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable n Age: (yrs.) median ±SD Weight (kg) mean ±SD Gender M/F	Values 2,672 cases, plus 926 controls Comparison sample - 41 yrs Cardiovascular disease sample – 52 yr Not reported 55% of controls M; 85% of CVD sample M											
	Generalizability to CMV drivers	Unclear												
Methods	Crash and violation rates of the control group per miles driven were compared to those with different medical conditions (including cardiovascular disease). Rates were age-adjusted.													
Statistical Methods	Statistical significance of difference between observed and expected crash and violation rates were determined by Mann-Whitney U test.													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
	Score = 8.5	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Expected and observed rates of crashes and violations/ 1,000,000 miles. (age-adjusted)													
Results	Expected crashes for cardiovascular disease group=9.0 / 1 million miles and observed = 14.6 /1 million miles (Table G-35). Difference significant at 0.001. Expected violation rate = 2.7/ 100, 000 miles and observed = 3.6/ 100,000 miles. Difference significant at *p* <0.005.													
Authors' Comments	Drivers with diabetes, epilepsy, cardiovascular disease, alcoholism, and mental illness averaged twice as many crashes per 100,000 miles of driving and 1 3/10 – 1 8/10 times as many violations per 100,000 miles as drivers in the comparison group on an age-adjusted basis.													

Table G-35. Observed and Expected Three-Year Crash and Violation Rates According to Diagnostic Category for Drivers with Medical Conditions Reviewed by the California Department of Motor Vehicles

Diagnostic Category	Driving Exposure	Crashes		Violations	
		Expected*	Observed†	Expected*	Observed†
	1,000,000 mi.	/ 1,000,000 mi.	/ 1,000,000 mi.	/ 100,000 mi.	/ 100,000 mi.
Epilepsy (445)‡	11.1	8.2	16.0	3.4	4.7
Cardiovascular disease (216) ‡	5.5	9.0	14.6	2.7	3.6
Diabetes (257)	9.0	8.7	15.5	3.3	4.6
Alcoholism (261)	8.2	6.8	11.3	2.5	4.6
Drug Usage (306) ‡	10.4	8.4	8.6	3.6	6.4
Mental Illness (231)	6.9	7.2	15.3	3.0	5.3
Miscellaneous(86)	2.2	7.4	20.7	2.8	4.9

* Age-adjusted rate based on 35,400,000 miles of driving exposure for weighted comparison sample (N-1646). Rates age adjusted by determination of age distribution according to decade and 10-yr. age-specific rates, for medical and comparison groups. Total crash & violation rates for comparison group then standardized by weighting of age-specific comparison-group rates with proportions of persons with medical conditions in corresponding age intervals.

† Crashes & violations resulting in initial report excluded to remove any spurious excess attributable to drivers with such incidents during 3 yr. before current report. Figures given represent rates for each group rather than mean individual rates & tend to underestimate differences between groups. However, to determine significance of difference, mean individual rates used & compared by means of Mann-Whitney U test. Differences between observed & expected rates significant at 0.001 level or higher for crashes & violations in all categories except for crashes in drug usage group ($p>0.05$) & for violations in cardiovascular-disease group ($p<0.05$).

‡ In additional 2 cases each, crash & violation information not available.

Ysander L. The safety of drivers with chronic disease. Brit J industry Med 1966; 23: 2-36														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
	✓													
Research Question	To determine extent a disease or related therapy are associated with traffic crashes or offenses; if drivers with a given disease are at higher risk for crash or offenses; if drivers with chronic disease are over-represented in road crashes and offenses													
Study Design	Retrospective case control													
Population	**Inclusion Criteria**	All licensed drivers in Gothenburg, Sweden through 12/31/1961 with a medically restricted license												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable n Age: (yrs.) mean ±SD Weight (kg) mean ±SD Gender M/F	Values 648 total; 97 with cardiovascular disease Ages reported categorically (Table G-36) Not reported 81% M											
	Generalizability to CMV drivers	Unclear												
Procedures	Controls were identified using a driver's license registry and matched to cases based on age, gender, and duration of holding a license. Controls were selected by serial number. Data was collected on investigated crashes and offenses from 1952-1961.													
Statistical Methods	Crash rates were calculated and compared as percentages													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
	Score = 8.5	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	Category= Moderate	**27**	**28**											
Relevant Outcomes Assessed	Crashes, serious traffic violations													
Results	1.7% of drivers with cardiovascular disease had a road crash, compared to 7.7% for the whole control series (Table G-37). 9.4% of drivers with cardiovascular disease and 15.3% of controls had a crash or serious driving offense.													
Authors' Comments	Drivers with medical conditions do not present an increased risk to road safety.													

Table G-36. Age Groups of Drivers in Group 1 with Cardiovascular Disease

Diagnostic Group	Age Group							Total
	18-20	21-25	16-30	31-40	41-50	51-60	>60	
Valvular heart disease	6	15	9	13	10	5		58
Coronary heart disease					4	3		7
Other heart disease	2	3		1	2	2		10
Hypertension	3	1	2	3	7	4	2	22
Total	11	19	11	17	19	15	5	97

Table G-37. Percentages of Drivers Involved in Road Crashes and Serious Driving Offenses

Investigation or Diagnostic Group	Drivers with Road Crashes (%)	Drivers with Road Crashes and Serious Driving Offences (%)
Whole investigation series except Group 4 m = 4.5 n = 612	4.1	9.8
Group 1 m = 4.6 n = 527	3.4	9.3
Group 2 m = 4.9 n = 58	1.7	3.4
Group 3 m = 4.1 n = 57	22.2	29.6
Diabetes m = 4.7 n = 256	5.0	11.7
Cardiovascular disease m = 5.1 n = 117	1.7	9.4
Renal disease m = 4.5 n = 120	2.5	7.5
Disease of the sense organs m = 4.7 n = 75	5.3	6.7
Whole control series	7.7	15.3

m = average observation period for possession of a driving license on special conditions (years)

n = number of drivers

Study Summary Tables (Key Question 2)

Studies of Risk Factors for Abdominal Aortic Aneurysm Rupture

Brown P, Zelt D, Sobolev B. The risk of rupture in untreated aneurysms: The impact of size, gender, and expansion rate. J Vasc Surg 2003; 37:280-4

Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			

Research Question	To establish the risk of rupture in relation to size of abdominal aortic aneurysm (AAA), gender, and expansion of the aneurysm	
Study Design	Cohort	
Population	**Inclusion Criteria**	Four hundred seventy-six patients were enrolled between 1976 and 2000 with follow-up until April 2002 with conditions considered unfit for surgery
	Exclusion Criteria	None reported
	Study population characteristics	Variable: Values n: 476 Age mean ±SD: 73.4 yrs Gender M/F: 377/99
	Generalizability to CMV drivers	Unclear
Methods	476 patients with AAA 5.0 cm or more were followed with computer tomographic scans every 6 months until rupture, surgery, death, or deletion from follow-up. Surgery was performed for rupture (n = 22), improved medical condition (n = 37), increase in size (n = 95), symptoms (n = 17), and other reasons (n = 24).	
Statistical Methods	To calculate the annual rate of rupture, the number of ruptures was divided by total number of patient years in follow-up. The effect size was measured using the Cox regression mode. The study used models with time-dependent covariates because the size of aneurysm changed over time.	

Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 8.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		N	Y	Y	Y	Y	Y	Y	Y	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	

Relevant Outcomes Assessed	Rate of AAA rupture
Results	Fifty ruptures occurred during the follow-up period (Table G-38). The average risk of rupture (and standard error) in male patients with 5.0 cm - 5.9 cm AAA (Table G-39) was 1.0% (0.01%) per year; in female patients with 5.0 cm – 5.9 cm AAA was 3.9% (0.15%) per year; in male patients with ≥6.0 cm AAA was 14.1% (0.18%) per year; and in female patients with ≥6.0 cm AAA was 22.3% (0.95%) per year. Table G-40 compares the expansion rate of AAAs that ruptured with non-ruptured AAAs. Differences in risk of rupture of AAA are shown in Table G-41.

Authors' Comments	The risk of rupture in male patients with AAA 5.0 cm to 5.9 cm is low. The four-time high risk of rupture in female patients with AAA 5.0 cm to 5.9 cm suggests a lower threshold for surgery be considered in fit women. The data regarding risk of rupture in patients with AAA ≥6.0 cm may allow more appropriate decision analysis for surgery in patients with unfit conditions with larger AAA.

Table G-38. Number of Patients, Ruptures, Time at Risk, Annual Rate, and Relative Risk According to Gender and Aneurysm Size

Description	*No. of patients*	*No. of ruptures*	*Time at risk (y)*	*Annual rate (standard error)*	*Relative risk (95 CI)*
Men, 5.0 – 5.9 cm	333	6	607	1.00 (0.01%)	1.0
Women, 5.0 – 5.9 cm	89	5	128	3.9% (0.15%)	4.0 (1.2,13.0)
Men, 6.0 cm or >	186	28	198	14.1% (0.18%)	14.3 (5.9,34.5)
Women, 6.0 cm or >	48	11	49	22.3% (0.95%)	22.6 (8.4, 61.1)

Table G-39. Rupture Rates when Sudden Deaths are considered to represent Rupture

Description	*No. of patients*	*Ruptures*	*Sudden death*	*Total*	*Annual rate (standard error)*	*Relative risk*
Men, 5.0 – 5.9 cm	33	6	5	11	1.8% (0.01%)	1.0
Women, 5.0 – 5.9 cm	89	5		6	4.7% (0.20%)	2.6
Men, 6.0 cm or >	186	28	3	31	15.6% (0.20%)	8.6
Women, 6.0 cm or >	48	11	4	15	30.5% (1.10%)	16.8

Table G-40. Mean and Median Expansion Rate (cm/y) among Patients with Ruptured and Non-ruptured AAA

Gained size				
	5.0 – 5.9 cm		*6.0 cm or greater*	
	Mean	*Median*	*Mean*	*Median*
Ruptured	0.44 (0.03)	0.33 (0.13,0.53)	0.84 (0.32)	0.55 (0.22,0.75)
Nonruptured	0.21 (0.09)	0.12 (0.05, 0.20)	0.39 (0.04)	0.27 (0.10, 0.51)
	t test: p<.05	Ratio at median: p <.1	*t* test: p <.01	Ratio at median: p<.1

Table G-41. Number of Patients, Ruptures, Time at Risk, Annual Rate According to Gender, and Aneurysm Size

Description	*No. of patients*	*No. of ruptures*	*Time at risk (person-years)*	*Annual rate (standard error)*

Men, 5.0 – 5.4 cm	301	4	500	0.8% (0.01%)
Women, 5.0 – 5.4 cm	71	5	60	5.1% (0.23%)
Men, 5.5 – 5.9 cm	217	2	226	0.8% (0.04%)
Women, 5.5 – 5.9 cm	58	0	97	

<table>
<tr><td colspan="14">Cronenwett J, Murphy T, Zelenock G, Whitehouse W, Lindenauer M, Graham L, Quint L, Silver T, Stanley J. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98(3):472-483</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="2">5</td></tr>
<tr><td colspan="3"></td><td colspan="3">√</td><td colspan="3"></td><td colspan="3"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="13">1) To determine the natural history of small aneurysms managed nonoperatively
2) To document the role of ultrasonography in the management of these lesions
3) To determine the ability of other potential risk factors to predict the likelihood of rupture</td></tr>
<tr><td>Study Design</td><td colspan="13">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">Patients in whom a deliberate decision had been made to pursue nonoperative management</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">Patients whose operation was delayed for scheduling purposes, patient convenience, or temporary acute illness. Also excluded were four patients who initially refused surgery and were followed for this reason.</td></tr>
<tr><td>Study population characteristics</td><td colspan="12"><u>Variable</u> <u>Value</u>
n 67
Age (yrs) mean±SD 72 yrs (range 50-91)
Weight Not reported
Gender M/F 53/14

Cardiac disease existed in 68% of patients and chronic obstructive pulmonary disease (COPD) was present in 24% of patients. Hypertension was prevalent, with 60% of patients taking antihypertensive medication other than diuretics. A family history of aortic aneurysm was in general poorly documented and known to be present in only 5% of patients (Table G-42).</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="13">Ultrasonography was performed with commercially available real-time sector and articulated arm contact (static) scanners. All patients were scanned in supine and in transverse and longitudinal planes. Although all patients had at least two ultrasound measurements separated by at least 1 month, 49 patients (73%) underwent multiple examinations at varying intervals. The first and last ultrasound measurements were used to calculate change and rate of change of aneurysm size.</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">The student two-tailed t test was used to calculate the mean expansion rates for aortic aneurysms grouped according to initial size. Cox proportional hazards regression was used to determine which covariate risk factors could statistically predict the time to aneurysm rupture.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="12">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 6.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="13">Risk factors for aneurysm rupture, aneurysm expansion rates</td></tr>
</table>

Results	The annual rate of aneurysm rupture was 6%, with an annual mortality rate caused by rupture of 5% and an annual mortality rate caused by coexistent disease of 6%. Thirty potential risk factors, including blood pressure, aneurysm size measured by ultrasonography, rate of aneurysm expansion, smoking, serum cholesterol levels, and cardiac, pulmonary, and renal risks, were analyzed by Cox proportional hazards regression to identify variables related to rupture. Aneurysm anteroposterior expansion rates varied from 0 to 1.5 cm/year but were different in aneurysms that ruptured. The interval between last ultrasound measurement and rupture in the 12 patients that had ruptured aneurysms was 8 + 4 months (Table G-43). Only diastolic blood pressure, initial aneurysm anteroposterior diameter, and degree of obstructive pulmonary disease were independently predictive of rupture. Predicted 5-year rupture rates varied from 2% when these risk factors were absent to 100% when all three risk factors were significant (Table G-44).
Authors' Comments	An alternative to frequent follow-up ultrasonography of patients with small aortic aneurysms would be to assess rupture risk at initial presentation based on an algorithm derived from the presence or absence of important risk factors. Obstructive pulmonary disease, initial aneurysm size, and diastolic hypertension must be evaluated prospectively to assess their accuracy in predicting small aneurysm rupture.

Table G-42. Risk Factors

	Rupture/expansion (n = 12)	*Nonrupture (n = 55)*	*p Value*
Age (yr)	72 ± 2	71 ± 1	0.96*
Blood pressure			
Systolic (mm Hg)	155 ± 8	154 ± 3	0.91*
Diastolic (mm Hg)	93 ± 5	87 ± 2	0.15*
Smoking			
Pack years	45 ± 9	35 ± 5	0.37*
Current packs/day	0.6 ± 0.2	0.5 ± 0.1	0.93*
Lipids			
Cholesterol (mg/dl)	206 ± 22	217 ± 11	0.67*
Triglyceride (mg/dl)	177 ± 53	167 ± 29	0.87*
Renal function			
Creatinine (mg/dl)	2.4 ± 0.9	1.3 ± 0.1	<0.01*
BUN (mg/dl)	33 ± 9	21 ± 2	<0.025*
Initial aneurysm size			
AP (cm)	4.0 ± 0.2	3.7 ± 0.1	0.24*
Transverse (cm)	3.9 ± 0.2	3.9 ± 0.1	0.91*
Last aneurysm size			
AP (cm)	5.1 ± 0.3	4.1 ± 0.2	<0.01*
Transverse (cm)	5.5 ± 0.3	4.5 ± 0.2	<0.01*
Interval between initial and final size (mo)	37 ± 8	26 ± 3	0.16*
Follow-up interval (mo)	48 ± 9	33 ± 3	0.09*
Expansion rate			
AP (mm/yr)	2.4 ± 1.8	1.7 ± 0.5	0.58*
Transverse (mm/yr)	4.5 ± 0.7	5.7 ± 1.8	0.75*
Proximal aorta diameter (cm)	2.3 ± 0.1	2.1 ± 0.1	0.15*
Initial aneurysm size ÷ proximal aortic diameter			
AP (ratio)	1.8 ± 0.1	1.7 ± 0.1	0.69*
Transverse (ratio)	1.8 ± 0.1	1.8 ± 0.1	0.58*
Aneurysm expansion rate ÷ proximal aortic diameter			
AP	0.10 ± 0.08	0.10 ± 0.05	0.99*
Transverse	0.20 ± 0.03	0.31 ± 0.09	0.54*
Symptoms at presentation			
Yes	75%	38%	<0.02†
No	25%	62%	
Aneurysm discovered by			
Physical examination	25%	47%	<0.04†
Radiograph	50%	16%	
Reason not operated			
Cardiac risk	58%	27%	0.11†
Small size	12%	32%	
Obstructive pulmonary disease			
None-mild	58%	90%	<0.01†
Moderate-severe	42%	10%	
Cardiac disease			
None	27%	33%	0.85†
Coronary artery disease	55%	50%	
Other cardiac disease	18%	17%	

*Student's two-tailed *t* test.
†χ^2 analysis.

Table G-43. Patients with Aneurysm Rupture or Acute Expansion

*Initial size (cm)**	*Final size (cm)**	*Interval of initial to final measurement (mo)*	*Event*	*Interval of final measurement to event (mo)*	*Outcome*
3.0 × 3.0	5.5 × 5.7	74	Rupture	1	Died home
3.0 × 3.4	3.0 × 4.0	28	Rupture	53	Died OR
3.5 × 3.5	5.0 × 5.3	48	Rupture	1	Died PO
3.5 × 4.0	5.0 × 5.0	35	Expansion	5	Died PO
4.0 × 3.5	4.8 × 6.2	48	Expansion	2	Alive
4.0 × 3.5	6.0 × 6.4	80	Expansion	3	Alive
4.0 × 4.0	4.2 × 4.2	22	Rupture	6	Died home
4.0 × 4.2	5.3 × 7.2	54	Expansion	3	Died PO
4.0 × 4.2	4.3 × 4.7	8	Expansion	1	Alive
4.7 × 5.0	5.0 × 5.2	7	Rupture	2	Died home
5.0 × 3.8	8.0 × 6.5	41	Rupture	15	Died home
5.0 × 5.0	5.0 × 5.0	4	Expansion	1	Alive

**Legend:* Dimensions: AP × transverse.
OR, In operating room; PO, postoperatively.

Table G-44. Aneurysm Rupture Rates Predicted by the Cox Proportional Hazards Model

	Risk level								
Risk factor (covariates)									
Diastolic blood pressure*	L	H	L	L	M	H	H	L	H
Initial aneurysm AP diameter†	L	L	H	L	M	H	L	H	H
Obstructive pulmonary disease‡	L	L	L	H	M	L	H	H	H
Time of follow-up									
	Rupture rate (%)								
1 (yr)	0	0	0	2	4	14	16	22	84
3 (yr)	0	4	4	10	18	28	54	66	98
5 (yr)	2	12	16	34	52	70	94	98	100

Legend: L, Low risk; M, medium risk; H, high risk.
*Diastolic blood pressure: L, 75 mm Hg; M, 90 mm Hg; H, 105 mm Hg.
†Initial aneurysm AP diameter: L, 3 cm; M, 4 cm; H, 5 cm.
‡Obstructive pulmonary disease: L, none; M, > 50% predicted FEV_1; H, < 50% predicted FEV_1.

Darling R, Messina C, Brewster D, Ottinger L. Autopsy study of unoperated abdominal aortic aneurysms. Cardiovascular Surgery 1976; 56(3):II 161-3														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
			√											
Research Question	Autopsy study of patients dying with untreated abdominal aortic aneurysms (AAA)													
Study Design	Cohort													
Population	**Inclusion Criteria**	Patients who died with unresected aneurysms												
	Exclusion Criteria	None reported												
	Study population characteristics	Variable Value Age (yrs) mean±SD 72 yrs Gender M/F 343/130 . Multiple risk factors by gender for ruptured and unruptured populations can be seen (Table G-45**)**												
	Generalizability to CMV drivers	Unclear												
Methods	Review of 24,000 consecutive autopsies during a 23-year period from 1952 through 1975 at the Massachusetts General Hospital													
Statistical Methods														
Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 6.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	N	N	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Relationship of size to rupture, survival times													
Results	There were 473 patients who died with surgically intact AAA (Table G-46). Of the multiple-risk factors considered, only size seemed to bear on the likelihood of AAA ruptures. Results for relationship of size to rupture show that even small aneurysms 4 cm or under can occasionally rupture and cause death (Table G-47 and Table G-50). Of more interest, however, is the similar rate of rupture in patients with aneurysms from 4.1 to 7.0 cm which is approximately 25%. However aneurysm from 7.1 to 10 cm had a rupture rate of about 45% and those over 10.1 cm had a mortality rate by aortic hemorrhage of 60%. Survival time was taken from the onset of severe back or acute abdominal pain (Table G-48**)**. The result suggests that at least in certain instances, as many as 50% of patients with AAA with symptoms suggesting rupture can survive at least 6 hours, time during which appropriate diagnosis and surgical treatment can be carried out. Over 40% lived more than 1 day after the onset of symptoms and about 25% lived more than 6 days. No data was available in 12% of patients. Of 58 patients followed 3 months to 10 years before death with known AAA, the majority died of the ruptured AAA (Table G-49).													

Authors' Comments	1) Small aneurysms do indeed rupture. 2) Contrary to previous studies, the incidence of rupture of AAA between 4 and 7 cm in this study is similar and significant (25%). 3) The authors were unable to find any factors other than size that seemed to bear on the likelihood of aneurismal rupture. 4) In a surgical environment with an expected mortality of less than 2%, abdominal aortic aneurysms as small as 4cm should be considered for resection.

Table G-45. Total Study Population of 473 Patients with Multiple-Risk Factors

	Unruptured (355)				*Ruptured (118)*			
Multiple Risk Factors	*Male*	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
Cardiac	166	65	231	65	56	19	75	64
Hypertension	91	57	148	42	35	17	52	44
Respiratory	84	7	91	26	26	4	30	25
Renal	36	10	46	13	15	4	19	16
Other vascular	83	35	118	33	15	2	17	14

There was no statistically significant difference between the unruptured and ruptured AAA group; the ages (average 72 years) were also comparable.

Table G-46. Percent of Un-resected Ruptured AAA Noted at Autopsy in 23-Year Period

	Unruptured	*Ruptured*	*Total*	*% Ruptured*
1952 – 1960	88	50	138	36
1961 – 1968	111	33	144	23
1969 – 1975	156	35	191	18
Total	355	118	473	

Table G-47. Relationship of the Size to Rupture in 473 Non-resected AAAs

Size (cm)	*Ruptured*	*Unruptured*	*Total*	*% Ruptured*
4 or under	19	182	201	9.5
4.1 – 5.0	15	49	64	23.4
5.1 – 7.0	21	62	83	25.3
7.1 – 10.0	31	37	68	45.6
10.1 or over	26	17	43	60.5
No size recorded	6	8	14	
Total	118	355	473	24.9

There appears to be little significant difference between the incidences of rupture of small aneurysms (4.1 – 7.0 cm).

Table G-48. Survival Time from Onset of Symptoms to Death in 118 patients with Non-resected Ruptured AAA

Survival time	*Number*	*%*
>6 hours	64	54
>24 hours	51	43
>6 days	29	25
>6 weeks	7	6
Not determined	14	12

Table G-49. Causes of Death in 52 Patients with Known AAA Followed from 3 Months to 10 Years without Surgery

Time	*Number dead*	*Ruptured AAA*	*Other causes*	*% Ruptured*

1 yr	21	9	12	43
5 yrs	39	18	21	46
10 yrs	52	27	25	52

Table G-50. Measurements of AAA at Autopsy in 52 patients with known Aneurysms Followed 3 Months to 10 Years without Surgery

Size (cm)	*Unruptured*	*Ruptured*	*Total*	*% Ruptured*
4 or under	11	1	12	8
4.1 – 5	6	2	8	25
5.1 – 7	3	3	6	50
7.1 – 10	4	7	11	64
10.1 or above	1	14	15	
Total	25 (48%)	27 (52%)	52	

<table>
<tr><td colspan="15">Faggioli G, Stella A, Gargiulo M, Taranti S, D'Addato M, Ricotta M. Morphology of small aneurysms: Definition and impact on risk of rupture. The American Journal of Surgery 1994; 168:131-135</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td></tr>
<tr><td></td><td colspan="2">√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">To investigate the impact of aneurysm morphology on the risk of rupture</td></tr>
<tr><td>Study Design</td><td colspan="14">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Patients undergoing repair of a small aneurysm (<5 cm in diameter)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Variable Value
n 135
Age (years) mean±SD 63±5 yrs
Gender M/F 98/37</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Prospective morphologic evaluation was performed in 135 consecutive cases of small (<5 cm) abdominal aortic aneurysm. Twelve cases (9%) were found to be ruptured and sent for emergency surgery. The remaining 123 patients were evaluated by ultrasonography, angiography, and intraoperatively during elective surgery. Ninety-six (78%) also underwent computerized tomography (CT) scanning. The evaluation assessed the thickness of the endoluminal thrombus and arterial wall as well as the presence of saccular outpouchings, or blisters, defined as small areas of localized further dilatation within the aneurysm. Also noted were any areas of impeding rupture, defined as discontinuity of the arterial wall with only a thrombus preventing rupture.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Results were examined by chi-square, Fisher's exact test, and multiple logistic regression analyses using commercially available software packages. Statistical significance was set at P <0.05.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 5.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Impact of aneurysm morphology on the risk of rupture</td></tr>
<tr><td>Results</td><td colspan="14">Blisters were discovered in intraoperatively in 12 aneurysms (Table G-51). Digital subtraction angiography (DSA) revealed 3 (25%) of these preoperatively. Eleven of the patients with blisters were examined preoperatively with CT scanning, which detected 3 (27%). Both endoluminal thrombus and wall thickness were measured by CT scan but not ultrasonography. The incidence of frank rupture among aneurysms <5 cm in diameter was 9 % (12/135) in this study. The incidence of impeding rupture was significantly greater in patients with blisters than in those without (71% versus 29%, P = 0.0001) (Table G-52 and Table G-53). The incidence of impeding rupture was similar whether the amount of endoluminal thrombus was more or less than 2 cm (57% versus 40%, P = 0.386). Rupture was</td></tr>
</table>

	more frequent when aneurismal walls were thicker or thinner than 0.3 cm (14% versus 20%, P = 0.719). In an analysis of logistic regression, the presence of a blister was the only independent morphologic predictor of impending rupture (P = 0.001).
Authors' Comments	In patients with small aneurysms, increased attention should be directed to the preoperative detection of blisters. The presence of a blister in the aneurysm wall is strongly correlated with impeding rupture. Wall and thrombus thickness are not associated with risk of impeding rupture. Aggressive treatment is necessary for aneurysms with blisters. The authors propose elective treatment of aneurysms <5 cm in young good-risk patients. Older patients with higher surgical risk should be investigated for the presence of a blister. If any are found, surgery may be considered. Since current diagnosis techniques cannot detect most blisters, ultra thin CT, spiral CT, or MRI should be evaluated for more accurate diagnosis.

Table G-51. Intraoperative Results

	N	*Blister*	*Endoluminal Thrombus (<2 cm)*	*Wall Thickness (<.03 cm)*
Impending rupture	7	5 (71%)*	4 (57%)†	1 (14%)†
Non-impending rupture	116	7 (6%)*	47 (41%)†	23 (2%)†
Total	123	12 (10%)	51 (41%)	24 (19%)

*p = 0.0001

†p= not significant

Table G-52. Logistic Regression for Risk of Impending Rupture

Variable	*Wald*	*P Value*
Endoluminal thrombus >2 cm	1.470	0.225
Wall thickness >0.3 cm	0.130	0.722
Blister	15.380	0.0001

Table G-53. Risk of Rupture of Small Aneurysms (<5 cm)

Study	*Year*	*No. of cases*	*Rupture*
Darling et al.	1977	64	23% (4.1 – 5 cm) 12% (all <5 cm)
Bernstein and Chan	1984	67	3%
Nevitt et al.	1989	130	0%

Limet et al.	1991	34	12%
Treiman et al.	1991	73	0%
Glimaker et al.	1991	110	1%
Ouriel et al.	1992	214	5%
Present study		135	9%

Fillinger M, Racusin J, Baker R, Cronenwett J, Teutelink A, Schermerhorn M, Zwolak R, Powell R, Walsh D, Rzucidlo E. Anatomic characteristics of ruptured abdominal aortic aneurysm on conventional CT scans: Implications for rupture risk. J Vasc Surg 2004; 39:1243-1252					
Key Questions Addressed	1	2	3	4	5
		√			
Research Question	To analyze anatomic characteristics of patients with ruptured abdominal aortic aneurysms (AAA), with conventional two-dimensional computed tomography (CT), including comparison with control subjects matched for age, gender, and size				
Study Design	Case control				
Population	**Inclusion Criteria**	Patients who had undergone CT scans (on file from 1990 to 2002) at Dartmouth-Hitchcock Medical Center before emergency AAA repair because of rupture or acute, severe pain (RUP group). Controls, matched for age and gender, had CT scans obtained electively for AAAs from the same time period (ELEC group).			
	Exclusion Criteria	Patients who underwent elective CT but had emergency surgery because of rupture or acute symptoms within a year were excluded from the ELEC group.			
	Study population Characteristics	Variable: Value n: 259 Age (years) average: 72 – 73 Gender M/F: 215 Additional baseline characteristics can be viewed in Table G-54.			
	Generalizability to CMV drivers	Unclear			
Methods	Aortic and iliac tortuosities were categorized as none, mild, moderate or severe. Aortic tortuosity was defined as none, mild (lumen center moves no more than one normal aortic diameter from renal to aortic bifurcation), severe (vessel makes a nearly right angle from 1 axial section to the next), or moderate (the remainder). Iliac tortuosity was more subjective and defined by agreement of observers on a "definition set" of films. As an approximation, for no or mild iliac tortuosity, the vessel major axis could not be more than twice the minor axis on a single axial CT section, and severe tortuosity was recorded when a vessel was visualized for a lengthy distance in the axial section (several vessel diameters) or had two visible cross-sections on a single axial section.				
Statistical Methods	Statistical analysis was performed with a standard software program (Statview, version 5.0; SAS Institute, Cary, NC). Groups were compared with analysis of variance with post hoc analysis for continuous variables or contingency table analysis for nominal variables. Values are reported as mean +/- SD. Association with rupture was evaluated with univariate and multivariate analyses, with stepwise regression with deletion of variables. P <0.05 was considered significant.				
Quality Assessment	**Internal Validity**				

Score = 7.88	1	2	3	4	5	6	7	8	9	10	11	12	13	
	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	NR	Y	
Category= Moderate	14	15	16	17	18	19	20	21	22	23	24	25		

Relevant Outcomes Assessed	Morphologic data and indices, multivariate analysis for statistically significant predictors of rupture risk
Results	Detailed results are presented in Table G-55 and Table G-56. In this study the major predictors for rupture (when patients were matched for gender and AAA diameter) were no or mild aortic tortuosity, diameter asymmetry and current smoking (Table G-57). Average diameter of ruptured AAAs in women was 5mm smaller than in men in this study.
Authors' Comments	Study limitations include only having anatomic data for AAAs in patients stable enough to undergo CT. Quality of CT scans was not uniform but adequate for the measurements in this study.

Table G-54. Demographic and Physiologic Variables

Variable	*Ruptured AAA (n = 122)*	*Elective CT (n = 137)*	P	*Diameter-matched ruptured AAA (n = 100)*	*Diameter-matched Elective CT (n = 100)*	P
Age (y)	72 ± 8	73 ± 8	.4	72 ± 8	73 ± 9	.5
Female gender (%)	21	23	.7	23	23	.9
Known heart disease (%)	61	61	.9	60	62	.8
Chronic obstructive pulmonary disease (%)	46	44	.7	48	41	.4
Smoking						
Current/former (%)	73	69	.3	75	68	.5
Current only (%)	46	24	.01	46	24	.02
Family history of AAA (%)	9	11	.6	8	12	.5
Diabetes mellitus	11	16	.7	13	15	.3
History of hypertension (%)	86	74	.02	85	72	.03
Blood pressure (mm Hg)						
Systolic	138 ± 40	135 ± 18	.5	137 ± 41	136 ± 19	.8
Diastolic	79 ± 21	78 ± 11	.6	78 ± 21	78 ± 11	.9
Creatinine concentration (mg/dL)	1.5 ± .8	1.4 ± 1.4	.5	1.5 ± .9	1.2 ± .8	.06

Table G-55. Morphologic Data

Variable	*Ruptured AAA (n = 122)*	*Elective CT (n = 137)*	P	*Diameter-matched Ruptured AAA (n = 100)*	*Diameter-matched elective CT (n = 100)*	P
Maximum AAA diameter (cm)*	6.5 ± 2	5.6 ± 1	.001	6.0 ± 1	6.0 ± 1	.8
Supraceliac aortic diameter (cm)	2.9 ± .5	2.7 ± .3	.001	2.9 ± .5	2.7 ± .3	.001
Suprarenal aortic diameter (cm)	2.6 ± .6	2.5 ± .4	.02	2.6 ± .5	2.5 ± .4	.2
Infrarenal aortic diameter, normal (cm)	2.7 ± .5	2.4 ± .3	.001	2.7 ± .6	2.4 ± .4	.001
Aortic bifurcation diameter (cm)	3.8 ± 2	3.1 ± 1	.001	3.5 ± 1	3.2 ± 1	.06
CIA normal diameter (right and left) (cm)	1.5 ± .6	1.6 ± .6	.3	1.4 ± .6	1.5 ± .7	.3
Infrarenal neck length (cm)	1.7 ± 1	2.1 ± 1	.02	1.7 ± 1	1.9 ± 1	.3
AAA only length (cm)	9.8 ± 3	9.5 ± 3	.5	9.5 ± 3	9.9 ± 2	.4
Renal-aotic bifurcation length (cm)	12.4 ± 3	12.1 ± 2	.4	12.1 ± 3	12.2 ± 2	.8
CIA normal length (right and left) (cm)†	3.6 ± 1.8	5.0 ± 1.7	.001	3.5 ± 2	4.9 ± 2	.001
Maximum thrombus thickness (cm)	2.6 ± 1	2.2 ± 1	.04	2.5 ± 1	2.3 ± 1	.4
Thrombus circumference (cm)‡	290 ± 100	290 ± 100	.7	290 ± 100	300 ± 90	.7
L3 transverse diameter (cm)§	4.6 ± .7	4.3 ± .4	.001	4.5 ± .5	4.3 ± .4	.005

AAA, Abdominal aortic aneurysm; *CIA*, common iliac artery.
*Maximum AAA diameter is based on the smaller "diameter" or axis if AAA cross-section is elliptical on axial CT sections.
†CIA normal diameter and normal length refer to nonaneurysmal segment, and was not available for all ruptured AAAs (n = 71 matched cases).
‡Circumference of AAA lumen contacting thrombus at point of its greatest extent (eg, 360 degrees is circumferential thrombus).
§Transverse diameter of body of L3 vertebra.

Table G-56. Calculated Indices

Variable	*Ruptured AAA (n = 122)*	*Elective CT (n = 137)*	P	*Diameter-matched ruptured AAA (n = 100)*	*Diameter-matched elective CT (n = 100)*	P
Maximum AAA/supraceliac diameter (cm)	2.3 ± .5	2.1 ± .3	.01	2.1 ± .6	2.2 ± .4	.2
Maximum AAA/suprarenal diameter (cm)	2.5 ± .7	2.3 ± .5	.006	2.4 ± .7	2.5 ± .5	.6
Maximum AAA/infrarenal diameter (cm)	2.4 ± .7	2.4 ± .5	.6	2.4 ± .7	2.6 ± .5	.08
Maximum AAA diameter/AAA length (cm)	.74 ± .4	.64 ± .2	.01	.72 ± .4	.65 ± .3	.2
AAA diameter/renal-aortic bifurcation length (cm)*	.56 ± .3	.48 ± .2	.02	.54 ± .3	.51 ± .2	.5
Maximum AAA/L3 transverse diameter (cm)†	1.4 ± .4	1.3 ± .2	.002	1.4 ± .3	1.4 ± .2	.2
Aortic tortuosity (moderate/severe) (%)	24	37	.2	23	45	.03
Iliac tortuosity (moderate/severe) (%)	61	59	.8	58	59	.6
Aortoiliac tortuosity index‡	4.5 ± 1.6	4.9 ± 1.6	.2	4.4 ± 1.6	5.1 ± 1.5	.02
AAA minor axis, anteroposterior (%)§	60	65	.5	59	67	.3
AAA diameter asymmetry (cm)‖	0.6 ± 0.7	0.4 ± 0.4	.02	0.6 ± 0.6	0.4 ± 0.4	.02

AAA, Abdominal aortic aneurysm.
*Distance from lowest renal artery to aortic bifurcation (see text).
†See Fig 1, *B*.
‡Quantitative index (see text).
§Percentage of cases in which minor axis of AAA cross-section is more closely oriented anteroposterior, rather than transverse. ‖Difference between major and minor AAA "diameter" on axial CT section.

Table G-57. Multivariate analysis*

Variable	*P*	*Odds ratio*	*95% confidence interval*
Aortic tortuosity (none/mild)†	.01	3.3	1.3 – 8.4
Aneurysm cross-sectional diameter asymmetry‡	.03	3.2	1.1 – 8.9
Currently smoking	.04	2.7	1.02 – 7.1

*Patients matched for gender, AAA diameter; †lower tortuosity worse; ‡ for 1-cm difference

Fillinger M, Marra S, Raghavan M, Kennedy F. Prediction of rupture risk in abdominal aortic aneurysm during observation: Wall stress versus diameter. J Vasc Surg 2003;37:724-32					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	To determine potential clinical relevance in terms of whether stress analysis may be more accurate than diameter for predicting rupture risk over time and whether the difference in wall stress can be detected far enough in advance to allow time for intervention				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with asymptomatic, infrarenal abdominal aortic aneurysms (AAAs) evaluated with spiral computer tomography (CT) and 3-D reconstruction as part of elective evaluation			
	Exclusion Criteria	Patients being evaluated for emergent repair of a possible symptomatic or ruptured AAA or were scheduled to undergo elective repair within 1 month			
	Study population characteristics	Observation Only Variable: Value n: 42 Age (yrs) mean±SE: 75±1 yrs Gender M/F: 16/26 Elective Repair Variable: Value n: 39 Age (yrs) mean±SE: 72±1 yrs Gender M/F: 18/21 Demographics were similar for patients who underwent observation without intervention, elective repair, or emergent surgery because of rupture or acute symptoms (Table G-58). Although patients selected for elective repair tended to be younger and had better renal function, there were no statistically significant differences between groups with respect to age, gender, heart disease, hypertension history, smoking history, chronic obstructive pulmonary disease, or creatinine concentration. The only variables that reached statistical significance were systolic and diastolic blood pressure, which was higher in the rupture/symptomatic group. Mean time between CT and intervention was similar for patients who underwent delayed elective repair and those who ultimately had acute symptoms or ruptured AAAs.			
	Generalizability to CMV drivers	Unclear			
Methods	CT scans were analyzed for patients with AAA when observation was planned for at least 6 months. AAA wall stress distribution was computationally determined in vivo with CT data, 3-D computer modeling, finite element analysis (nonlinear hyperelastic model depicting aneurysm wall behavior), and blood pressure during observation.				
Statistical Methods	All statistical evaluation was performed with standard software programs (Statview 5.0, SAS Institute, Cary, NC, for all statistics other than receiver operating characteristic (ROC) curve area analysis, which was performed with SPSS II, SPSS, Chicago, IL). The three groups (observation, elective repair, rupture/symptomatic) were compared with analysis of variance (ANOVA), with post hoc analysis for				

<table>
<tr><td></td><td colspan="14">continuous variables or contingency table analysis for nominal variables. The values are reported as mean ±SE unless otherwise specified. Survival analysis (Kaplan-Meier method with log-rank test) was used to evaluate freedom from rupture or emergency surgery over time.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 8.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">AAA diameter and wall stress, rupture risk over time</td></tr>
<tr><td>Results</td><td colspan="14">Analysis included 103 patients and 159 CT scans (mean follow-up, 14 ± 2 months per CT). Forty-two patients were observed with no intervention for at least 1 year (mean follow-up, 28 ± 3 months). Elective repair was performed within 1 year in 39 patients, and emergent repair was performed in 22 patients (mean, 6 ± 1 month after CT) for rupture (n = 14) or acute severe pain. Significant differences were found for initial diameter (observation, 4.9 ± .1 cm; elective repair, 5.9 ± .1 cm; emergent repair, 6.1 ± .2 cm; p <0.0001) and initial peak wall stress(38 ± 1 N/cm^2, 42 ± 2 N/cm^2, 58 ± 4 N/cm^2, respectively; p <0.0001), but peak wall stress appeared to better differentiate patients who later required emergent repair (elective vs. emergent repair: diameter, 3% difference, p = 0.5; stress, 38% difference, p <0.0001). ROC curves for predicting rupture were better for peak wall stress than for diameter. With proportional hazards analysis, peak wall stress and gender were the only significant independent predictors of rupture.</td></tr>
</table>

Authors' Comments	For AAAs under observation, peak AAA wall stress seems superior to diameter in differentiating patients who will experience catastrophic outcome. Elevated wall stress associated with rupture is not simply an accurate event near the time of rupture. Overall, stress analysis is practical and feasible.

Table G-58. Demographics

Variable	*Observation only (n = 42)*	*Elective repair (n = 39)*	*Rupture or symptoms (n = 22)*	P
Age (y)	75 ± 1	72 ± 1	75 ± 2	.1
Female gender (%)	26	21	41	.2
Known heart disease (%)	52	69	47	.2
Hypertension (%)	36	28	35	.7
Systolic BP (mm Hg)	138 ± 3	134 ± 2	150 ± 6	.02
Diastolic BP (mm Hg)	76 ± 2	80 ± 2	84 ± 2	.03
Smoking (current) (%)	26	21	36	.5
COPD diagnosis (%)	24	43	38	.2
Creatinine concentration (mg/dL)	1.3 ± .12	1.0 ± .05	1.5 ± .4	.07
Follow-up (mo)	28 ± 3	4 ± 1	5 ± 1	<.01

BP, Blood pressure; *COPD*, chronic obstructive pulmonary disease.

<table>
<tr><td colspan="8">Guirguis E, Barber G. The natural history of abdominal aortic aneurysms. Am J Surg 1991; 162: 481-483</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="2">3</td><td>4</td><td colspan="2">5</td></tr>
<tr><td></td><td>√</td><td colspan="2"></td><td></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="7">To study the rate of expansion of Abdominal Aortic Aneurysms (AAA) and to examine the risk of rupture in relation to their size</td></tr>
<tr><td>Study Design</td><td colspan="7">Cohort (referral-based study)</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="6">All patients presenting to the same vascular surgeon at Ottawa Civic Hospital from January 1984 - April 1990, with an AAA that was initially managed nonoperatively. This included patients who refused recommended surgery.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="6">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="6">Variable Value
N 300
Age (years) mean 70.4 (range 46-92)
Gender M/F 211/89

There were 203 (68%) smokers, 68 (23%) on hypertensive medication, and 7 (2%) diabetics. Only 19(6%) were on β-blockers.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="6">Unclear</td></tr>
<tr><td>Methods</td><td colspan="7">Patients were enrolled in the study as soon as they first presented and followed up prospectively for the duration of the study period or until the occurrence of an intervention event (operation, rupture, death, or loss to follow-up). Majority (94%) of the patients was followed up with serial ultrasonography, and the remaining patients were followed up with CT scans. Patients underwent serial ultrasonography or CT scanning at 6-month intervals.</td></tr>
<tr><td>Statistical Methods</td><td colspan="7">The Kaplan-Meier life-table analysis was used to calculate the cumulative survival of all patients and the cumulative incidence of aneurysm rupture in relation to initial diameter. The exact binomial test was used to calculate the statistical significance of the difference in aneurysm rupture rates of varying sizes.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 6.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="7">Aneurysm expansion rate, risk of rupture of AAA by size</td></tr>
<tr><td>Results</td><td colspan="7">Patients were followed for a mean duration of 34 months (range: 2.5 to 76 months). The mean initial AAA diameter was 4.1 cm (range: 2.5 to 9.3 cm) The majority (81%) of the patients had aneurysm less than 5 cm diameter at initial diagnosis. Aneurysm expansion rate among the 208 patients who underwent more than one ultrasound or computed tomographic (CT) scan, the diameter of the aneurysm increased by a median of 0.3 cm per year. Results for rupture risk show a 6-year cumulative</td></tr>
</table>

	incidence of rupture of 1% and 2% among patients with aneurysm less than 4.0 cm and 4.0 to 4.9 cm in diameter, respectively (p >0.05).In comparison, the 6-year cumulative incidence of rupture was 20% among patients with aneurysms greater than 5.0 cm in diameter (P <0.004).The 6-year cumulative survival of patients in the study was 93%.Of the 300 patients studied, 14 (9 men and 5 women) had a rupture of their aneurysm during the study interval; of these patients 4 survived emergency aneurysm repair. Based on the most recent radiologic examination, the median and mean aneurysm diameters of the 14 patients who sustained rupture while being observed were 6.5 and 6.6 cm, respectively. Twelve (86%) of these 14 patients had aneurysms 5cm or more in diameter prior to rupture.
Authors' Comments	Abdominal aortic aneurysms expand at a median rate of 0.3 cm per year. Risk of rupture of abdominal aortic aneurysms < 5.0 cm is substantially lower than the risk of rupture of aneurysms ≥ 5.0 cm in diameter.

Jones A, Cahill D, Gardham R. Outcome in patients with a large abdominal aortic aneurysm considered unfit for surgery. Br J Surg 1998; 85: 1382-1384					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	An analysis of data to assistant in decision to operate on high risk patients with Abdominal Aortic Aneurysms (AAA)				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with an intact AAA of 5 cm or greater in diameter referred to one surgeon at a district hospital serving a population of approximately 250,000			
	Exclusion Criteria	None reported			
	Study population characteristics	Aneurysm repair Variable — Value n — 133 Age (yrs) mean — 73 yrs (range 56 – 85) Non-operated Variable — Value n — 57 Age (yrs) mean — 81 yrs (range 69 – 93) Patients over 80 years old comprised 22 % of all referrals (Table G-59).			
	Generalizability to CMV drivers	Unclear			
Methods	Clinicians were asked to refer all patients with an AAA even if unfit or elderly. One hundred and ninety-two patients with an intact AAA of 5 cm or more in anteroposterior or transverse diameter were seen in 9 years (May 1985 to April 1994). One hundred and thirty-three patients underwent elective operation for an intact aneurysm. Selection was based on clinical judgment using no predetermined criteria. Fifty nine patients were rejected for elective operation and data were available for 57 at a minimum of 2 years. For analysis, patients who did not have aneurysm repair were divided into two groups: those with aneurysm 5.0-5.9 cm (n = 25) and patients with an AAA of 6.0 cm or greater (n = 32). The initial size of the aneurysm was the sole basis for this grouping; serial measurements were generally not done.				
Statistical Methods	Survival was calculated by the Kaplan-Meier method.				

Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 9.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	

Relevant Outcomes Assessed	Survival, rupture risk

Results	The elective operation rate in octogenarians was eight (19%) of 43 compared to 125(84%) of 149 for patients aged under 80 years. The main reasons for denying AAA repair were: cardiovascular disease (25 patients), old age (15), malignancy (8), respiratory disease (6), and patients' wishes (3). Patients rejected because of old age were rejected on functional state not absolute age. At the close of the study 50 of the 57 patients who did not have aneurysm repair had died. Median survival was 18 (range 1-90) months. Twenty (35%) suffered rupture at a median interval of 18 (range 1-38) months. Rupture risk **(**Table G-60**):** the risk of rupture within 3 years was 28 (95 per cent confidence interval 12-49) per cent for 5.0 – 5.9 cm AAAs and 41 (24-59) per cent for AAAs of 6 cm or greater. In 133 elective AAA operations in fit patients the 30-day mortality was 3 per cent.
Authors' Comments	The risks of rupture within 3 years of diagnosis of an AAA of 5 cm or greater exceeds the expected operative mortality rate for fit patients. However, the majority of patients unfit for surgery died from other causes and only a few benefited from aneurysm repair.

Table G-59. Patients Details and Causes of Death

	Aneurysm size (cm)	
	5-0 to 5-9	*≥ 6.0*
Total no. of patients	25	32
Mean age (years)	79	82ǂ
Gender ratio (M:F)	18:7	25:7
Mean AAA size (cm)	5.4	7.3
Rupture	7	13*
Deaths		
o Cause uncertain	2	1
o Other disease	11	17
Alive	5	2*

* One patient survived rupture. AAA, abdominal aortic aneurysm. ǂP<0.05 versus 5.0 – 5.9 cm AAA (Student's t test)

Table G-60. Interval to Rupture

Interval within which rupture occurred	*Size at entry (cm)*	*Time until rupture (months)*	*Cumulative percentage ruptured**
AAA 5.0 – 5.9 cm			
1 year	5.7	6	8 (1-26)
	5.5	9	
2 years	5.6	18	24 (9-45)
	5.0	20	
	5.4	21	
	5.5	23	
3 years	5.5	30	28 (12-49)
AAA ≥ 6.0 cm			
1 year	8.5	1	16 (5-33)
	14.0	2	
	9.5	3	
	7.0	4	
	7.0	8	
2 years	8.0	13	28 (14-47)

	6.0	15	
	8.2	16	
	8.0	18	
3 years	9.0	25	38 (21-56)
	7.0	32	
	6.6	34	
4 years	6.3	38	41 (24-59)

*Values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm.

Lederle F, Johnson G, Wilson S, Ballard D, Jordan W, Blebea J, Littooy F, Freischlag J, Bandyk D, Rapp J, Salam A. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. JAMA 2002;287(22):2968-2972					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	To determine the incidence of rupture in patients with large abdominal aortic aneurysm				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients diagnosed as having abdominal aortic aneurysm (AAA) of at least 5.5 cm in diameter by ultrasonography or computer tomography (CT) within 3 months prior to enrollment and for whom elective repair was not expected in the next 6 months because of medical contraindications to surgery or patient refusal			
	Exclusion Criteria	Patients with symptoms or radiological evidence of rupture; previous aortic surgery; dissection of the thoracic aorta; known condition associated with secondary AA (e.g., Marfan disease); or death expected in the next 30 days			
	Study population characteristics	Variable: Value N: 198 Age (yrs) mean±SD: 73.9±7.2 yrs Gender M/F: 197/1 Nearly all patients had a history of smoking (Table G-61), reflecting both the veteran population and the population at risk for AAA. Most were elderly and had high rates of co-morbidities, especially coronary artery disease and chronic obstructive pulmonary disease.			
	Generalizability to CMV drivers	Unclear			
Methods	One hundred and ninety-eight patients enrolled from April 1995 - April 2000 and were followed up through July 2000. Follow-up began at enrollment by telephone call to the study's central office confirming eligibility and consent. Subsequent measurements of AAA were obtained by ultrasonography at 6-month intervals throughout the study. The maximum outside AAA diameter was used, as determined by the radiologist's reading at the participating medical center. Follow-up ended at the time of elective AAA repair, following successful repair of rupture, at death, or at the end of the study.				
Statistical Methods	Rupture rates were generated by product-limit estimates (SAS PROC LIFETEST, SAS Institute Inc, Cary, NC). Cox regression models (SAS PROC PHREG) to assess baseline variables as predictors of rupture and logistic regression models (SAS PROC LOGIST) that included last measured AAA diameter to assess AAA enlargement rate as predictor of rupture.				

Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 7.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	N	N	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes	Incidence of rupture													

Assessed	
Results	Outcome ascertainment was complete for all patients. There were 112 deaths (57%) and the autopsy rate was 46%. Forty-five patients had probable AAA rupture. Cumulative incidence of possible, probable, or definite rupture for 3 strata of initial AA diameter is shown in Table G-62. Cumulative incidence of rupture by 3 strata of attained AAA diameter is shown in Table G-63. The 1-year incidence of probable rupture by initial AAA diameter was 9.4% for AAA of 5.5 to 5.9 cm, 10.2% for AAA of 6.0 to 6.9 cm (19.1% for the subgroup of 6.5-6.9 cm), and 32.5% for AAA of 7.0 cm or more. Much of the increased risk of rupture associated with initial AAA diameters of 6.5-7.9 cm was related to the likelihood that the AAA diameter would reach 8.0 cm during follow-up, after which 25.7% ruptured within 6 months.
Authors' Comments	The rupture rate is substantial in high-operative risk patients with AAA of at least 5.5 cm in diameter and increases with larger diameters.

Table G-61. Patient Characteristics at Time of Enrollment (N = 198)*

Characteristic	
Age, y	73.9(7.2)
Male,%	99.5
Race,%	
White	89.4
Black	9.6
Weight, kg	80.5(20.5)
Height, cm	175.4(10.4)
Ever smoked,% †	94.9
Current smoker, %	33.8
Hypertension, %	66.2
Systolic blood pressure, mm Hg	132.0(20.3)
Chronic obstructive pulmonary disease, %	57.6
Coronary artery disease, %	70.7
Myocardial infarction, %	46.5
Cardiovascular disease, %	25.3
Claudication, %	28.4
Diabetes, %	22.3
Cancer, %	23.2
B-Blocker use, %	22.2
AAA diameter, cm	6.6(1.0)
Family history of AAA, %	14.7
Thoracic aortic aneurysm, %	4.5
AAA with iliac artery involvement, %	22.3
AAA with renal artery involvement, %	10.2
Reasons that elective AAA repair was not planned, % ‡	
Patient refusal	42.6
Poor medical condition	81.3
Advanced age	24.0
Cardiac condition	67.8
Pulmonary condition	48.5
Mental health status	5.3

* Data are given as mean (SD) unless otherwise specified. AAA indicates abdominal aortic aneurysm.

† More than 100 cigarettes over lifetime.

‡ Patients could have more than one reason

Table G-62. Cumulative Incidence of Rupture by Initial AAA Diameter*

Type of Rupture Event	Follow-up, mo						
	6	12	18	24	30	36	42
Patients with AAA 5.5-5.9 cm (n = 61)							
Definite (n = 7)	3.5	5.5	11.8	16.4	22.4	22.4	. . .
Probable (n = 11)	3.5	9.4	17.7	22.1	27.6	27.6	. . .
Possible (n = 15)	3.5	9.4	22.4	26.5	35.7	35.7	. . .
Patients with AAA 6.0-6.9 cm (n = 85)							
Definite (n = 13)	3.8	7.5	7.5	16.5	24.2	24.2	32.7
Probable (n = 17)	5.0	10.2	10.2	18.9	26.5	32.1	47.2
Possible (n = 19)	5.0	10.2	10.2	21.4	28.8	37.9	51.7
Patients with AAA ≥ 7.0 cm (n = 52)							
Definite (n = 15)	11.0	27.9	34.4	39.5	. . .	. . .	. . .
Probable (n = 17)	11.0	32.5	38.7	43.4	. . .	. . .	. . .
Possible (n = 18)	12.8	34.0	40.0	44.6	. . .	. . .	. . .

* Data are given as percentages. AAA indicates abdominal aortic aneurysm; ellipses, data not shown (for instances in which <10 patients remained in observation at the beginning of the interval). Definite ruptures were confirmed by autopsy, surgery, or computed tomographic scan. Probable ruptures were defined as all definite ruptures plus cases of death with symptoms consistent with AAA rupture and cases of repair of symptomatic unruptured AAA. Possible ruptures were defined as all probable ruptures plus cases of sudden unexplained/unwitnessed deaths.

Table G-63. Cumulative Incidence of Rupture by Attained AAA Diameter*

Type of Rupture Event	Follow-up, mo				
	6	12	18	24	30
Patients with AAA 5.5-5.9 cm (n = 61)					
Definite (n = 4)	3.6	6.4	15.0	. . .	. . .
Probable (n = 6)	3.6	12.0	20.0	. . .	. . .
Possible (n = 7)	3.6	12.0	25.3	. . .	. . .
Patients with AAA 6.0-6.9 cm (n = 113)					
Definite (n = 6)	2.0	3.8	6.5	13.5	13.5
Probable (n = 8)	3.0	6.1	8.8	15.6	15.6
Possible (n = 11)	3.0	7.4	10.0	20.2	20.2
Patients with AAA ≥ 7.0 cm (n = 107)					
Definite (n = 25)	11.0	23.4	28.7	31.8	37.1
Probable (n = 31)	11.9	29.2	34.1	37.0	47.1
Possible (n = 34)	14.0	30.9	35.7	41.0	50.5

*Data are given as percentages. Patient could be evaluated in more than 1 stratum in this analysis, but events are counted only once. AAA indicates abdominal aortic aneurysm; ellipses, data not shown (for instances in which <10 patients remained in observation at the beginning of the interval). Definite ruptures were confirmed by autopsy, surgery, or computed tomographic scan.

Nevitt M, Ballard D, Hallett J. Prognosis of abdominal aortic aneurysms: A population based study. NEJM 1989; 321(15):1009-1014														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**									
		√												
Research Question	1) To assess the rate of change in the size of abdominal aortic aneurysms among patients who were examined with serial ultrasound studies 2) To assess the risk of subsequent rupture among persons in whom unruptured aneurysms had initially been documented on ultrasonography													
Study Design	Cohort													
Population	**Inclusion Criteria**	Patients residing in Rochester, MN, with medical records (outpatient and inpatient records of each provider) in whom an abdominal aortic aneurysm was initially diagnosed between January 1, 1951, - December 31, 1984												
	Exclusion Criteria	None reported												
	Study population characteristics	Rochester residents who had undergone one or more abdominal ultrasound examinations that documented the presence of an aneurysm were followed. Of the 370 residents with aneurysm initially diagnosed from 1951 through 1984, 181 had aneurysm documented by ultrasound examination												
	Generalizability to CMV drivers	Unclear												
Methods	This population-based study was possible because the diagnoses and surgical procedures of essentially all Rochester residents are indexed, and the original medical records can be retrieved readily for review. In this study, Rochester residents who had undergone one or more abdominal ultrasound examinations that documented the presence of an aneurysm were followed; for purposes of comparability with previous studies, the maximal transverse diameter (anteroposterior or lateral) of the aneurysm (in centimeters) was abstracted from radiology report from each ultrasound. For all patients, the complete medical records in the community were followed through July 1, 1988, to identify aneurysm repair, rupture, or death.													
Statistical Methods	The absolute change in the size of aneurysm for each patient with more than one ultrasound study was determined as the final diameter minus the initial diameter. General linear regression analysis and the Kruskal-Wallis test were used to assess the association between characteristics at the time of initial ultrasound examination and the subsequent mean and median rates of change in size. Kaplan-Meir survival analysis and Cox proportional-hazards analysis were used to assess the risk of rupture and importance of risk factors for rupture after the initial documentation of an aneurysm by ultrasound study.													
Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 7.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	Y	Y	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	

Relevant Outcomes Assessed	Rate of change in size, risk of rupture in relation to initial size, and risk of rupture in relation to the rate of change in size.
Results	Among the 103 patients who underwent more than one ultrasound study, the diameter of aneurysm increased by a median of 0.21 cm per year. Only 24% had a rate of expansion of 0.4 cm or more per year (see Table G-64).Among the 176 patients who had an unruptured aneurysm at the time of the initial ultrasound study, the cumulative incidence of rupture was 6% after 5 years and 8% after 10 years. However the risk of rupture over 5 years was 0% for 130 patients with an aneurysm >5 cm in diameter and 25% for the 46 patients with an aneurysm ≥5 cm in diameter. All patients who had ruptures had aneurysms ≥5 cm in diameter at the end of the rupture. Previous referral-based studies have usually reported mean values for aneurysm growth (see Table G-65).
Authors' Comments	For aneurysms <5 cm in diameter, the risk of rupture is considered lower than has been reported previously. However, the risk of rupture is substantial for aneurysms ≥5 cm in diameter.

Table G-64. Distribution of the Rate of Change in the Diameter of Abdominal Aortic Aneurysms from Initial to Final Ultrasound Examination in 103 Residents of Rochester, Minn*

Detection and changes in diameter (cm/yr)	Number of patients	% of patients
Decrease of > 0.20	4	3.9
Decrease of 0.01- 0.20	4	3.9
No change	9	8.7
Increase of ≤ 0.20	31	30.1
Increase of 0.20- 0.39	30	29.1
Increase of 0.40- 0.59	9	8.7
Increase of ≥ 0.60	16	15.5
Total	103	100

*The subjects had aneurysms that were initially diagnosed from 1951 to 1984, underwent at least two ultrasound examinations and were followed through July 1, 1998.

Table G-65. Median and Mean Rates of Change in the Diameter of Abdominal Aortic Aneurysms, According to Initial Size for Aneurysms initially Less than 5 cm in Diameter

Initial Diameter	Median Rate of Change†						Mean Rate of Change†		
	Rochester	Munich	Oxford‡	Rochester	Munich	Oxford‡	Bernstein and Chan	Cronenwett ET AL.	Sterpetti ET AL.
cm	Cm / yr no. patients								
< 3.0	0.20 (20)	0.08 (3)	-	0.21 (20)	0.08 (3)	-	-	-	-
3.0-3.9	0.21 (40)	0.13 (22)	-	0.26 (40)	0.19 (22)	-	0.39 (32)	0.79(T) 0.19 (AP)§	0.25¶
4.0 – 4.9	0.26 (31)	0.13 (10)	-	0.46 (31)	0.18 (10)	-	0.36 (35)	0.45 (T) 0.50 (AP)§	0.40 (4.0-4.4) 0.56 (4.5-4.9)¶
Total (<5.0)	0.21 (91)	0.13 (35)	0.22(27)	0.32 (91)	0.17 (35)	0.28(27)	0.37 (67)	0.57 (T) 0.22 (AP)(67)‖	0.48 (43)**

* Data from Munich are from Kremer et al., those from Oxford are from Collin et al., and those form the US referral centers are from Bernstein and Chan, Cronenwett et al., and Sterpetti et al. T denotes transverse diameter, and AP anteroposterior diameter. All other data are based on maximal diameter (T or AP).

† The numbers of patients are indicated in parentheses when these data were reported or could be derived from information provided in the published study.

‡ Data were available only for the total group with aneurysms of 5cm or less in diameter.

§ The numbers of patients in each size category were not reported.

¶ Published data were available for the following sizes: 3.5 to 3.9, 4.0 to 4.4, and 4.5 to 4.9 cm. The numbers of patients in each size category were not reported.

‖Published data provided the mean expansion rates for the total group with aneurysms of 6cm or less in diameter. The reported average expansion rates for all aneurysms 6cm or less in diameter weighted equally were 0.45 cm per year (T) and 0.30 cm per year (AP).

** Published data provided the mean expansion rates for the total group with aneurysms of less than 6 cm in diameter.

<table>
<tr><td colspan="8">Reed W, Hallett J, Damiano M, Ballard D. Learning from the last ultrasound. A population-based study of patients with abdominal aortic aneurysm. Arch Intern Med 1997; 157: 2064-2068</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="2">3</td><td>4</td><td colspan="2">5</td></tr>
<tr><td></td><td>√</td><td colspan="2"></td><td></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="7">To assess prognosis of patients with unruptured abdominal aortic aneurysms</td></tr>
<tr><td>Study Design</td><td colspan="7">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="6">Patients were Rochester residents with AAA diagnosed by ultrasound between January 1, 1974, and December 31,1988</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="6">Patients with clinical evidence of rupture at the time of initial ultrasound</td></tr>
<tr><td>Study population characteristics</td><td colspan="6">Variable Value
N 181
Age (yrs) mean 74 (range 48-97)
Gender M/F 112/69</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="6">Unclear</td></tr>
<tr><td>Methods</td><td colspan="7">The authors used data from the population-based cohort of residents of Rochester, MN, diagnosed as having abdominal aortic aneurysm. Patients had at least one ultrasound measurement. The average number of ultrasound performed for each patient was 2.5. Analysis of a cohort defined by size category at "last ultrasound" was undertaken to assess rupture risk and growth rate. Cohort defined by last ultrasound (Table G-66). For the clinician, every ultrasound is for at time the 'last ultrasound", therefore the authors constructed a cohort with1 entry for each ultrasound.</td></tr>
<tr><td>Statistical Methods</td><td colspan="7">Correlation among growth rate and subsequent growth rates were analyzed using the Pearson correlation coefficient. For all analyses that included growth rate, cases were excluded if time from start to date of next ultrasound was less than 90 days. This exclusion eliminated the extreme results for growth rate, which were an artifact of a very short interval between ultrasound examinations. Mean growth rate according to ultrasound growth period were assessed using analysis of variance. Rupture risk by size cohort within the last ultrasound cohort was compared with Kaplan-Meier analysis using the log rank tests.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 7.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="7">Aneurysm growth rate, estimated rupture risk by last ultrasound</td></tr>
<tr><td>Results</td><td colspan="7">Median overall aneurysm growth was 0.21 cm/ year (Table G-67).Initial growth rate of an aneurysm did not predict subsequent growth rate. Excluding comparisons that included the overall growth rate, no correlations were significant. Growth rate was not influenced by maximal diameter of the AAA. The correlation between size at last ultrasound and growth rate was -0.06 (p=.38) (Table G-68). When only the first growth period after diagnosis by ultrasound was considered, correlation between initial</td></tr>
</table>

	growth rate and size at diagnosis also was not significant (r= -0.12; p=.22). A strong relation between size at last ultrasound and rupture risk was apparent. The smaller number of person-years for large aneurysms reflects the increased likelihood that patients would undergo elective surgery, and the greater number of ruptures (Table G-69). Table G-70 shows how growth rates compare with case series and other population-based studies. Much variability was observed among these studies.
Authors' Comments	The most clinically useful approach to estimating the risk of abdominal aortic rupture is according to size at last ultrasound. Aneurysm growth rate is predicted neither by size nor by initial growth rate. Limitations of this study include lack of evaluating other variables, such as comorbidity, which may be related to growth rate or rupture risk.

Table G-66. Constructing the "Last Ultrasound" Event Table

Step 1: Extract Original Data (Patient A)

	Diameter of AAA at Ultrasound, cm				
Ultrasound No.	1	2	3	4	5
Patient A	3.1	3.4	3.8	4.3	5.7
Ultrasound dates	1/6/88	7/1/89	12/1/90	12/1/91	10/27/92

Termination date: 11/27/92. Termination type: aneurysm rupture.

Step 2: Construct Last Ultrasound Event Table Using Above Data From Patient A

Observation	Start Size, cm	Date	End Size, cm	Date	Event
A1	3.1	1/6/88	3.4	7/1/89	None
A2	3.4	7/1/89	3.8	12/1/90	None
A3	3.8	12/1/90	4.3	12/1/91	None
A4	4.3	12/1/91	5.7	10/27/92	None
A5	5.7	10/27/92	NA	11/27/92	Rupture

**AAA indicates abdominal aortic aneurysm; NA, not applicable.*

Table G-67. Growth Rates of Aneurysms Defined by Ultrasound Growth Period

Growth Period	Growth Rate, cm/y			No. of Cases
	Mean (SD)	Median	Range	
1	0.16 (0.49)	0.15	−1.62 to 1.86	99
2	0.23 (0.56)	0.14	−0.69 to 3.80	66
3	0.30 (0.76)	0.10	−0.79 to 4.23	43
4	0.18 (0.60)	0.19	−1.65 to 1.65	32
5	0.31 (0.51)	0.30	−0.48 to 1.67	17
6	0.10 (0.30)	0.10	−0.57 to 0.45	11
7	0.44 (0.32)	0.43	0.10 to 0.89	5
Overall	0.30 (0.45)	0.21	−0.89 to 1.92	100

**First growth period is the period between first and second ultrasound examinations. Nth growth period is the period between nth and nth+1 ultrasound examinations.*

Table G-68. Growth Rates by Initial Size within "Last Ultrasound" Cohort

Size, cm	Growth Rate, cm/y			No. of Cases
	Mean (SD)	Median	Range	
<3	0.23 (0.29)	0.20	−0.48 to 0.99	41
3.00-3.99	0.23 (0.61)	0.14	−1.04 to 4.22	106
4.00-4.99	0.17 (0.42)	0.10	−0.95 to 1.65	94
5.00-5.99	0.43 (0.94)	0.29	−1.62 to 3.80	23
6.00-6.99	0.19 (0.29)	0.12	−0.16 to 0.70	7
≥5.00	0.29 (0.90)	0.22	−1.64 to 3.80	32
≥6.00	−0.08 (0.67)	0.00	−1.64 to 0.70	9

Table G-69. Estimate of Rupture Risk by Aneurysm Size at "Last Ultrasound"

Size, cm	Intervals	Ruptures	Person-Years	Ruptures/ Patient-Year	95% CI
<3	58	0	111	0.00	0.00-0.08
3.00-3.99	145	0	185	0.00	0.00-0.05
4.00-4.99	148	1	148	0.007	0.00-0.05
5.00-5.99	61	4	38	0.11	0.01-0.21
6.00-6.99	28	5	9	0.26	0.07-0.46

**CI indicates confidence interval. P<.001 for comparison of all categories.*

Table G-70. Growth Rates for Aneurysms

Source	Growth Rate, cm/y		Study Type	No. of Subjects	Size-Growth Relation
	Median	Mean			
Cronenwett et al[7]	...	0.45	REF	67	NR
Glimaker et al[4]	0.00	0.38	POP	187	Yes
Collin et al[3]	0.22	...	POP	50	No
Bernstein et al[6]	...	0.40	REF	49	NR
Bengtsson et al[15]	0.80	...	REF	88	Yes
MacSweeney et al[16]	0.13	...	REF	43	No
Current study	0.21	0.30	POP	176	No

**REF indicates referral case series; POP, population-based study; yes, aneurysm size correlates positively with growth rate; and NR, not recorded.*

<table>
<tr><td colspan="14">Schewe C, Schweikart H, Hammel G, Spengel F, Zoller N, Zoller W. Influence of selective management on the prognosis and risk of rupture of abdominal aortic aneurysms. Clin Investig 1994; 72: 585-591</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="4">5</td></tr>
<tr><td></td><td>√</td><td colspan="3"></td><td colspan="3"></td><td colspan="4"></td></tr>
<tr><td>Research Question</td><td colspan="13">To investigate the influence of selective management on the prognosis and risk rupture of abdominal aortic aneurysms</td></tr>
<tr><td>Study Design</td><td colspan="13">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">Patients in whom an abdominal aortic aneurysm was detected by abdominal ultrasound at the Medizinische Poloklinik University in Munich from 1976 to 1993</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">Inflammatory aneurysms and cases with ectasia of the entire aorta were excluded</td></tr>
<tr><td>Study population characteristics</td><td colspan="12">Variable — Value
n — 199
Age (yrs) mean — Males – 69.2 yrs (range 38.5-84 yrs)
Females – 73.4 yrs (range 57.5-90 yrs)
Gender M/F — 169/30

The median aneurismal diameter at entry was 3.60 cm (mean 3.73 cm, range 2.60cm-9.05 cm).
Large aneurysms (diameter >5 cm) were present in 34 of the 199 patients (17.1%) at the initial examination.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="13">199 individuals with abdominal aortic aneurysms that were managed selectively based on aneurysm size, expansion rate, and patient characteristics were followed for 17 years. Patients with an average aneurismal diameter below 5cm were managed nonoperatively unless the aneurysm was symptomatic. These patients were followed up by clinical visits and ultrasound examinations every 6 months. Surgery was advised when the aneurysm became symptomatic, when the expansion rate exceeded 0.5cm per 6-month period, or when the average diameter reached 5cm or more, provided that no contraindications were present. Ends-points were rupture of the aneurysm, aneurysm repair, death, or last contact with a physician.</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">BMDP statistical software was used for statistical calculations. The overall rate of rupture was assessed by the Kaplan-Meier product limit method. Mann-Whitney/ Wilcoxon's U test were used to compare possible predictors of rupture among ruptured and unruptured aneurysms. The survival rate was compared to age-matched German male population (data from government population statistics for 1990) using life-table calculations by the actuarial method of Cutler-Ederer. Only male population survival rates were chosen for comparison since 84% of the patients groups were men. Univariate and multiple regression analysis were used to assess possible variables affecting the expansion rate. Average values of expansion rates for groups of different initial diameters were calculated and compared using Wilcoxon's U test and Kruskal-Wallis test, respectively</td></tr>
<tr><td rowspan="2">Quality Assessment</td><td>Internal Validity</td><td colspan="12">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td>Score = 7.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
</table>

		Y	Y	Y	Y	Y	Y	N	N	NR	Y			
	Category= Moderate	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Aneurysm expansion rate; rate of rupture; possible predictors of rupture; long-term survival													
Results	The expansion rate was significantly correlated with the initial diameter and the diastolic blood pressure (best subset multiple regression analysis: r = 0.403; P <0.001). A correlation with the systolic blood pressure was found only in univariate analysis (r = 0.236; P = 0.011). There was no significant correlation between expansion rate and age, amplitude of blood pressure, serum cholesterol level, low- and high- density lipoprotein, or smoking habits (Table G- 71). Rupture occurred in eight cases; aneurysms were > 5 cm in diameter at the last exam, and six were > 5 cm at the initial measurement. The resulting overall 5-year cumulative rate of rupture was 7.3%. Results for aneurysm expansion rate can be seen in Table G-72. The expansion rates ranged from no increase in diameter to 1.60 cm/year (median 0.18cm/year). Median expansion rate of small aneurysms (diameter < 5cm, n = 123) was 0.17 cm /year. Larger aneurysms (diameter ≥ 5cm, n = 11) grew at a median rate of 0.30 cm /year (P = 0.012). The 5-year survival rate was 66.7 %.													
Authors' Comments	Larger diameter and higher diastolic blood pressure are important risk factors for expansion of abdominal aortic aneurysms. Selective management of abdominal aortic aneurysms based on aneurysms size, expansion rate, and patient's characteristics may result in a low rate of rupture.													

Table G- 71. Comparison of Possible Predictors of Rupture between Patients with Rupture and Patients with Unruptured Aneurysms (U test)

Variable	Ruptured ($n=8$)	Nonruptured ($n=191$)	P
Systolic blood pressure (mmHg)	176.00 ± 37.81	153.85 ± 23.31	0.198
Diastolic blood pressure (mmHg)	98.00 ± 16.43	86.46 ± 12.47	0.135
Amplitude of blood pressure (mmHg)	78.00 ± 24.89	67.39 ± 18.12	0.458
Mean expansion rate (cm/year)[a]	0.47 ± 0.23	0.23 ± 0.26	0.013
Diameter at last measurement (cm)	7.28 ± 1.70	6.14 ± 1.56	0.036
Diameter at initial measurement (cm)	5.58 ± 1.92	3.92 ± 1.21	0.007
Total cholesterol (mg/dl)	235.20 ± 34.25	246.32 ± 62.13	0.627
Smoking history (pack-years)	14.00 ± 15.16	23.17 ± 24.88	0.476
Age at entry (years)	71.91 ± 7.92	69.77 ± 8.54	0.479
Observation period (years)	3.63 ± 2.76	2.65 ± 3.23	0.177

[a] Expansion rates were determiend in 134 patients who underwent sequential ultrasound examinations (7 with ruptured aneurysms and 127 without)

Table G-72. Abdominal Aneurysm Expansion by Diameter

Diameter (cm)	*n*	*Mean annual rate of change (cm/year)*	*Median annual rate of change (cm/year)*	*Maximum expansion rate (cm/year)*
2.5 – 2.9	24	0.13	0.09*	0.82

3.0 – 3.9	69	0.23	0.19	1.05
4.0 – 4.9	30	0.31	0.23	1.60
>5	11	0.39	0.30*	1.00

* Difference between 2.5 – 2.9 cm and >5 cm, p< 0.05

Mean values are given in addition to median growth rates despite the skewed distribution of expansion rates to enable comparability to literature.

<table>
<tr><td colspan="15">Stenbaek J, Kalin B, Swedenborg J. Growth of thrombus may be a better predictor of rupture than diameter in patients with abdominal aortic aneurysms. Eur J Endovasc Surg 2000; 20:466-469</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td></tr>
<tr><td></td><td colspan="2">√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the relationship between diameter, surface and thrombus area in abdominal aortic aneurysms (AAA) ≤5 cm</td></tr>
<tr><td>Study Design</td><td colspan="14">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Patients with initial AAA diameters ≤5 cm</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Variable Value
n 67
Age (years) mean 67 (range 54-79)
Gender M/F 43/24</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Sixty-seven patients with AAA underwent at least 2 computed tomography (CT) examinations. At the point of maximal diameter, surface area and thrombus area were calculated and related to rupture, or impeding rupture, during follow-up.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Mann-Whitney U -test and chi-square with Fisher's exact test were used for statistical analysis.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 6.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">At the point of maximal diameter, surface area and thrombus area were calculated and related to rupture, or impeding rupture</td></tr>
<tr><td>Results</td><td colspan="14">The mean increase in measured diameter, surface area and thrombus area was .34cm/year, 1.9 cm^2, and 1.7 cm^2 per year respectively. There were no obvious differences in diameter, surface area or thrombus area between those that ruptured and those that did not (Table G-73).Therefore, further analysis concentrated on the rate of increase of these parameters. There was a significantly higher increase of thrombus area ($p < 0.05$) among the seven patients that ruptured. No corresponding significant difference in growth of diameter was seen (Table G-74). Patients with AAA >2 cm^2/year and whose thrombus area increased >1.5 cm^2/year were more likely to rupture (6/24 vs. 1/23) (Table G-75).</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The principal findings of this study are that no patient without a thrombus experienced rupture and those that rupture had a significantly faster growth of their thrombus. This study supports the concept that presence of thrombus in general and growth of thrombus in particular is associated with an increased risk of rupture. The precise mechanisms behind the association remain to be clarified. Whether thrombus growth is a better predictor than surface growth is a question which will have to</td></tr>
</table>

	be confirmed in larger studies.

Table G-73. AAA >4 cm at last examination. Measures of diameter, surface and thrombus areas (mean and range)

	Rupture *n=7*	*No Rupture* *n = 45*	*p-value*
Max diameter (cm)	5.2 (4.3 – 7.0)	5.1 (4.2 – 6.7)	ns
Surface area (cm²)	20.6 (14.5 – 33.6)	19.3 (12.2 – 35.4)	ns
Thrombus area (cm²)	12.9 (5.9 – 19.8)	9.3 (0 – 21.3)	ns

Table G-74. Growth patterns of AAA >4 cm diameter at last examination (mean and range)

	Rupture *n=7*	*No Rupture* *n = 45*	*p-value*
Increase of diameter (cm/year)	0.67 (0 – 1.5)	0.36 (0 – 1.7)	0.14
Increase of surface area (cm²/year)	4.3 (0.9 – 9.0)	2.1 (0 – 6.5)	0.09
Increase of thrombus area (cm²/year)	4.9 (0 – 9.7)	1.6 (-2.5 – 8.5)	<0.05

Table G-75. Number of patients with rupture vs. no rupture separated into growth rate and total area and thrombus area

Annual increase	Total no. of patients	Rupture	% rupture	*p*-value
Total area ($n=52$)				
$\leq 2\ cm^2$/year	25	2	8 (2/25)	0.27
$>2\ cm^2$/year	27	5	19 (5/27)	
Thrombus area ($n=47$)*				
$\leq 1.5\ cm^2$/year	23	1	4 (1/23)	0.10
$>1.5\ cm^2$/year	24	6	25 (6/24)	

*The total number of patients in this group is less than 52 because five patients were not given contrast on the last CT examination and calculations of thrombus areas could therefore not be made.

Studies of Risk Factors for Rupture of a Thoracic Aortic Aneurysm

Clouse W, Hallett J, Schaff H, Gayari M, Ilstrup D, Melton J. Improved prognosis of thoracic aortic aneurysms. A population-based study. JAMA 1998; 280: 1926-1929					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	To ascertain whether the previously reported poor prognosis for individuals with thoracic aneurysm has changed with better medical therapies and improved surgical techniques that can now be applied to aneurysm management				
Study Design	Population-based cohort				
Population	**Inclusion Criteria**	All 133 patients with the diagnosis of degenerative thoracic aneurysms among Olmsted County, Minnesota, residents between 1980 and 1994. Diagnosis of thoracic aortic aneurysm was accepted if a focal aortic dilatation (1.5 times larger than normal local aorta) was identified and confirmed by radiographic studies, operation, or autopsy.			
	Exclusion Criteria	Acute aortic dissection, traumatic aortic lacerations, annular dilatation without ascending aortic enlargement, and penetrating atheromatous lesions without aneurismal change			
	Study population characteristics	Variable: n; Age (years) mean; Gender M/F Value: 133; 69.0 – overall average age at diagnosis; 75.9 - average age for women at diagnosis; 62.8 – average age for men at diagnosis; 65/68 The anatomic location was delineated as ascending aortic or aortic arc disease alone in 40%, descending thoracic aortic disease alone in 31%, and both in 20%. The mean diameter (± SD) of these degenerative aneurysms was 4.9 ± 0.2cm (median, 4.7 cm). Size at diagnosis did not differ by gender (mean, 4.9 ± 1.2 cm among women and 4.9 ± 1.6 cm among men). Seventy-nine percent of the 105 aneurysms were less than 6cm at initial diagnosis, while 21% of the 28 aneurysms were 6cm or larger.			
	Generalizability to CMV drivers	Unclear			
Methods	This population-based study was possible because all Olmsted County residents with a recognized thoracic aortic aneurysm could be identified, and their complete medical records could be retrieved for review. All medical records were reviewed for each resident in whom an initial diagnosis of thoracic aortic aneurysm was made between January 1, 1980 and December 31, 1994. They were compared with a previously reported cohort of similar patients between 1951 and 1980. All patients were followed up through their complete medical records until death, emigration from the community, or to February 1, 1997, to identify aneurysm repair, rupture, or death.				
Statistical Methods	Summary rates were directly adjusted to the (5-year) age distribution of the white population of the United States in 1990. Ninety-five percent confidence intervals (CIs) were calculated around the point estimates by assuming a Poisson error distribution. Secular tends were modeled with Poisson regression. The Kaplan-Meier method was used to estimate survival and to ascertain probability of rupture. Expected survival rates were calculated from life tables of the Minnesota white population.				

	Associations between continuous risk factors and rupture risk were evaluated with Cox proportional hazards models. The Cox model was also used for multivariate assessment of risk factors for rupture, including time-dependent risk factors.													
Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**												
	Score = 7.75	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	N	Y	Y	Y	NR	Y			
	Category= Low	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Incidence, cumulative rupture risk, rupture risk as a function of aneurysm size, long-term survival													

Results	The 133 residents with thoracic aortic aneurysms were identified from a population averaging about 100,000.The overall incidence rate, age-and gender-adjusted to the 1990 US white population, was 10.4 per 100,000 person-years (95% CI, 8.6- 12.2). Incidence rates increased dramatically with age, and age-adjusted rates were greater for men than women. After the 1980-1984 study, age-adjusted incidence rates increased more than 3-fold compared with the previous study from 1951 to 1980. Rupture occurred in 28 (21%) of the 133 cases. The cumulative risk of rupture was 20 %(95% CI 12%-28%) after 5 years. Seventy-nine percent of rupture occurred in women (P = 0.01). When the 3 significant factors at diagnosis (gender, symptoms, and age) were placed in a Cox multivariate model, the factors that remained associated with increased rupture risk were female gender (risk ratio, 6.8; 95% CI, 2.56- 19.3); P = 0.01) and symptoms at recognition (risk ratio, 7.0; 95% CI, 2.56-19.3; P = 0.01). Age at diagnosis was not associated with rupture risk when included in the multivariate model (risk ratio, 1.03; 95% CI, 0.99-1.07; P = 0.16). The relationship of size to the cumulative probability of rupture did not achieve statistical significance in the univariate analysis (P = 0.48) but the observed probabilities of rupture risk were consistent with increasing size. The 5-year risk of rupture as function of aneurysm size at recognition was for aneurysms less than 4cm in diameter: 0%; for aneurysm 4 to 5.9 cm: 16%; and for aneurysms ≥ 6 cm: 31 %. Long-term survival results show eighty deaths occurred among patients with degenerative thoracic aortic aneurysms. Overall 5-year survival improved to 56% (95% CI, 48% - 66%) between 1980 and 1994 compared with only 19% between 1951 and 1980 (P <0.01). The leading cause of death in this cohort was rupture of the thoracic aortic aneurysm, which accounted for 39% of the deaths.
Authors' Comments	Overall survival for thoracic aneurysms has improved significantly in the past 15 years. In this population, elderly women represent an increasing portion of all patients with clinically recognized thoracic aortic aneurysms and constitute the majority of patients whose aneurysm eventually ruptured. The association between female gender and rupture risk remains unexplained by our current understanding of aneurysm pathogenesis. Although the mean age at diagnosis was 13 years older for women than men, the mean size at recognition was similar. However, the surgical intervention rate of women was one half the rates for men. Because women were on average 76 years old at diagnosis compared with men who were only 63 years old, advanced age may have influenced the decision for less operative intervention in the female cohort.

<table>
<tr><td colspan="15">Coady M, Rizzzo, J, Goldstein L, Elefteriades J. Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. Cardiology Clinics 1999; 17 (4): 1-25</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td></td><td colspan="3">√</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">Observations on thoracic aneurysms</td></tr>
<tr><td>Study Design</td><td colspan="14">Review</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">600 patients followed serially for aortic pathology at the Yale Center for Thoracic Aortic Disease.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13"></td></tr>
<tr><td>Study population Characteristics</td><td colspan="13"></td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unknown</td></tr>
<tr><td>Methods</td><td colspan="14">Observational</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">N/A</td></tr>
<tr><td rowspan="6">Quality Assessment</td><td>Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Score = 6.75</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Size of aneurysm at rupture.</td></tr>
<tr><td>Results</td><td colspan="14"><u>Authors' observations at Yale Center for Thoracic Aortic Disease</u>
➢ TAA patients sustained a rupture or acute dissection at a median aortic size of 6.0 cm.
➢ Descending or arch aneurysms ruptured or dissected at a median size of 6.0 cm.
➢ Descending or thoracoabdominal aneurysms ruptured or dissected at a median size of 7.2 cm.
➢ 3 of 25 patients with Marfan's syndrome suffered acute dissections or ruptures at sizes <5 cm in diameter.
➢ Blood pressure did not appear to influence the rate of aortic expansion.
➢ Presence of chronic dissection was a significant predictor for more rapid aneurysmal growth.
➢ Survival rates for aneurysms with diameter of >6 cm: 85%-1 year, 64%-5 years. Mortality primarily related to the aneurysmal disease process.
➢ Patients with descending TAs had lower long-term survival (82% 1 year; 39% 5-year) then did patients with ascending aneurysms (87% 1-year; 77% 5-year), (P <0.04).
➢ Neither surgical status nor the first-imaged size significantly affected survival. However, because surgically treated patients tend to have more critical illness, these findings point to a beneficial survival effect from surgery.</td></tr>
</table>

	➢ Survival rate decreases (59% 5 year survival at size ≥6 cm) as first-imaged aneurysm size increases ➢ Evidence for a rising incidence of dissection or rupture with expanding aneurysm size. Median size at time of rupture or dissection was 6.0 cm for ascending aneurysms and 7.2 for descending aneurysms. Multivariable regression analysis to isolate risk factors for acute dissection of rupture revealed that size ≥6.0 cm increased the probability of these events for ascending aneurysms (P = 0.005). For descending aneurysms, this probability increased by 43.0% at a size ≥7.0 cm. (P = 0.012) ➢ Overall growth rate for TAA = 0.12 cm/year Growth rate of aortic aneurysms in familial nonsyndromic TAA = 0.22 cm/year. The familial TAA growth rate is significantly faster than the growth rate of patients belonging to the sporadic (0.03 cm/y, p ≤0.012) or Marfan syndrome groups (0.10 cm/y, P ≤0.035) Genetic etiology permits more rapid aortic dilatation. ➢ More than one gene may play a role in transmission of aortic aneurysms. Majority of pedigrees seem to be autosomal dominant, an additional 23.1% autosomal dominant or X-linked dominant. 27% recessive transmission. ➢ Results for actuarial survival showed patients with type B dissection were 65% at 1 year and 50% at 5 years. For medically treated patients, survival was 47% at 1 year and 28% at 5 years. Patients with type A dissections are typically younger (mean age of 56.5 years in Yale series) and elastic tissue degeneration is the more common histologic observation. Most common involve connective tissue disorders such as Marfan or Ehlers-Danlos syndromes. In patients without connective tissue disorders, media degeneration appears to be primarily related to wear-and-tear of aging and that induced by arterial hypertension. <u>Review of Data on last 100 consecutive patients with an acute descending aortic dissection (1988 to 1998)</u> • 9 died during initial hospital admission (6 deaths directly related to the aorta and branch vessel involvement, 3 deaths due to failure of other organ systems) • 91 survivors of initial hospital admission ➢ 60 benign courses with no specific aortic complications ➢ 31 had complications related to the aorta; 8 patients had rupture (5 were operated at time that rupture was recognized, 3 did not undergo operation); 17 had complications due to occlusion of important branch vessels of the aorta (5 involved the lower extremity, 5 involved renal vessels, 5 affected spinal cord, 2 involved abdominal visceral arteries); 4 patients manifest failure to control pain despite maximal medical management; 12 manifested expansion of the aorta on early follow-up while still in the hospital; 6 patients extended the dissection proximally into aortic arch during initial admission ➢ 42/100 came to operation for aortic replacement: 22 during the first 30 days for early complications of dissection; 20 late after presentation (30 days to 10 years); 32 patients had direct aortic grafts; 6 underwent fenestration of the aorta; 4 had thrombo exclusion procedure; 6 of the surgical patients died. Nonlethal postoperative surgical complications included paraplegia or paraparesis in 6 patients and respiratory insufficiency in 12 patients.
Authors' Comments	Perhaps the most well documented risk factor for aortic rupture is increasing aneurysm size. Authors review documented rupture or dissection of ascending or arch aneurysms at a median size of 6 cm and descending or thoracoabdominal aneurysm rupture or dissection at a median size of 7.2 cm. Most recent evidence for growth rate of TAA is 0.12cm/year.

Davies R, Goldstein L, Coady M, Tittle S, Rizzo J, Kopf G, Elefteriades J. Yearly rupture or dissection rates for thoracic aortic aneurysm: Simple prediction based on size. Ann Thorac Surg 2002; 73:17-28					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	To estimate the yearly rupture or dissection rate of thoracic aortic aneurysms (TAA) and the risk factors predictive of rupture				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with thoracic aortic aneurysm treated at Yale University School of Medicine; aortic size at least 3.5 cm and age older than 6 years at presentation; absence of congenital aortic malformations (for example, aortic coarctation); at least one size measurement before referral for operative repair			
	Exclusion Criteria	Patients with preexisting dissection			
	Study population characteristics	Variable: Value n: 304 Age (years) median: 65.8 Gender M/F: 179/125 28 patients had been diagnosed with Marfan syndrome. Additional patient characteristics are shown in Table G-76.			
	Generalizability to CMV drivers	Unclear			
Methods	Data on patients was prospectively entered into the database of the Yale Center for Thoracic Aortic Disease. Three hundred four patients were dissection-free at presentation; their natural history was followed for rupture, dissection, and death.				
Statistical Methods	The method of statistical analysis included chi square test for comparisons of dichotomous risk factors (history of coronary artery disease, congestive heart failure, abdominal aortic aneurysm) with negative outcomes (rupture, dissection, death); Mantel-Haenszel chi square test for comparisons taking into consideration disease severity (cardiac disease, pulmonary disease, progressively larger aneurysms, and so forth); and the Wilcoxon test for comparisons of continuous variables with negative outcomes($p < 0.05$). Logistic regression analysis of the cumulative incidence was used to evaluate the influence of risk factors for rupture or dissection. Life-table estimates (Kaplan-Meier) were calculated using the LIFETEST procedure of SAS 6.12 for Power PC with log –rank difference between strata. Average yearly rates were calculated from this life-table analysis using – ln (X) / 5 where X is the complication-free survival after 5 years.				
Quality Assessment	**Internal Validity**	**Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies**			
	Score = 6.75	**1**: Y; **2**: Y; **3**: Y; **4**: Y; **5**: N; **6**: Y; **7**: N; **8**: N; **9**: NR; **10**: Y; **11**: ; **12**: ; **13**:			
	Category= Low	**14**: ; **15**: ; **16**: ; **17**: ; **18**: ; **19**: ; **20**: ; **21**: ; **22**: ; **23**: ; **24**: ; **25**:			

Relevant Outcomes Assessed	Rupture or dissection rate and rupture risk; risk factors predictive of rupture; aneurysm growth rate; long-term survival
Results	Five-year survival in patients not operated on was 54%. Among the 92 hard end realized in serial follow-up of these patients were 55 deaths, 13 documented ruptures, and 24 documented new acute aortic dissections. For aneurysms greater than 6 cm in diameter, rupture occurred at 3.7% per year, rupture of dissection at 6.9% per year, death at 11.9%, and death, rupture, or dissection at 15.6% per year. At size greater than 6.0 cm, the odds ratio for rupture was increased 27-fold ($p = 0.0023$). Mean rate of rupture or dissection: small aneurysms: 2%; aneurysm 5.0 to 5.9 cm: 3%; aneurysm ≥ 6cm in diameter: 6.9%. Risk of rupture alone: for small aneurysms: near zero; aneurysm 5.0 to 5.9 cm: 1.7% per year; aneurysm ≥ 6cm in diameter: 3.6% per year. Risk of rupture, dissection, or death from all causes: for aneurysm 5.0 to 5.9 cm: 6.5%; aneurysm ≥ 6cm in diameter: 14.1%. The mean aortic growth rate was 0.10 cm/year. Aortic size was a very strong predictor of rupture dissection, and mortality. Significant univariate predictors of rupture included location of the aneurysm in the descending or thoracoabdominal aorta and a history of abdominal aortic aneurysm. In addition, male gender conferred significant protection from rupture. (Table G-78, Table G-79, Table G-80, and Table G-82)
Authors' Comments	This study indicated that thoracic aneurysm is a lethal disease with aneurysm size having a profound impact on rupture, dissection, and death. Patients with an aneurysm exceeding 6 cm can expect a yearly rate of rupture or dissection of at least 6.9% and a death rate of 11.8%. Elective surgical repair usually restores survival to near normal. This analysis strongly supports careful radiologic follow-up and elective, preemptive surgical intervention for the otherwise lethal condition of large thoracic aortic aneurysm.

Table G-76. Demographic Data on 304 Patients with TAA[a]

Variable	n	%	Mean	Median	Range
Gender (male)	179	58.9			
Age at presentation (y)			59.8	65.8	8.8 to 93.7
Initial aortic size (cm)			5.9	4.7	3.5 to 11.0
Radiologic follow-up (mo)			43.1	31.6	0.0 to 262.6
Marfan syndrome	28	9.2			
Aneurysm size					
3.5 to 3.9 cm	33	10.9			
4.0 to 4.9 cm	133	43.8			
5.0 to 5.9 cm	78	25.7			
≥ 6 cm	60	19.7			
Aneurysm location					
Ascending	219	72.0			
Arch	18	5.9			
Descending	28	9.21			
Thoracoabdominal	39	12.8			
Hypertension (n = 240)	142	59.1			
Cardiac disease (n = 219)	96	43.8			
Tobacco use (n = 220)	81	36.8			
Pulmonary disease (n = 225)	47	20.9			
Carotid disease (n = 209)	23	11.0			
Renal disease (n = 220)	30	13.6			
Coronary artery disease (n = 304)	82	27.0			
Congestive heart failure (n = 304)	34	11.2			
Stroke or transient ischemic attacks (n = 304)	25	8.2			
Abdominal aortic aneurysm (n = 304)	31	10.2			

[a] Total may not add up to 100% because of rounding.

Table G-77. Distribution of 92 End Points[a]

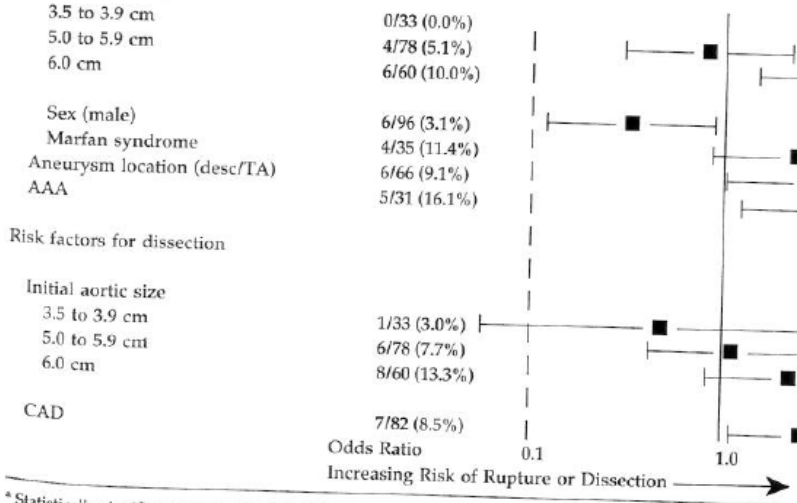
Events	No. patients
Dissection, rupture and death	2
Dissection, rupture (no death)	2
Dissection, death (no rupture)	5
Rupture and death (no dissection)	4
Rupture alone	5
Dissection alone	15

Death alone	44

▫Some patients satisfied multiple end points, leading to the total of the 92 specific events

Table G-78. Univariate Analysis of Risk Factors Predictive of Rupture Dissection

Risk Factor	Complication Rate	Odds Ratio (with 95% CI)	p Value
Risk factors for rupture			
Initial aortic size			
3.5 to 3.9 cm	0/33 (0.0%)		
5.0 to 5.9 cm	4/78 (5.1%)	1.303	0.198
6.0 cm	6/60 (10.0%)	3.762[a]	0.666
			0.014[a]
Sex (male)	6/96 (3.1%)	0.365[a]	0.044[a]
Marfan syndrome	4/35 (11.4%)	2.839	0.071
Aneurysm location (desc/TA)	6/66 (9.1%)	3.243[a]	0.032[a]
AAA	5/31 (16.1%)	4.663[a]	0.003[a]
Risk factors for dissection			
Initial aortic size			
3.5 to 3.9 cm	1/33 (3.0%)	0.337	0.272
5.0 to 5.9 cm	6/78 (7.7%)	0.963	0.939
6.0 cm	8/60 (13.3%)	2.192	0.081
CAD	7/82 (8.5%)	2.370[a]	0.028[a]

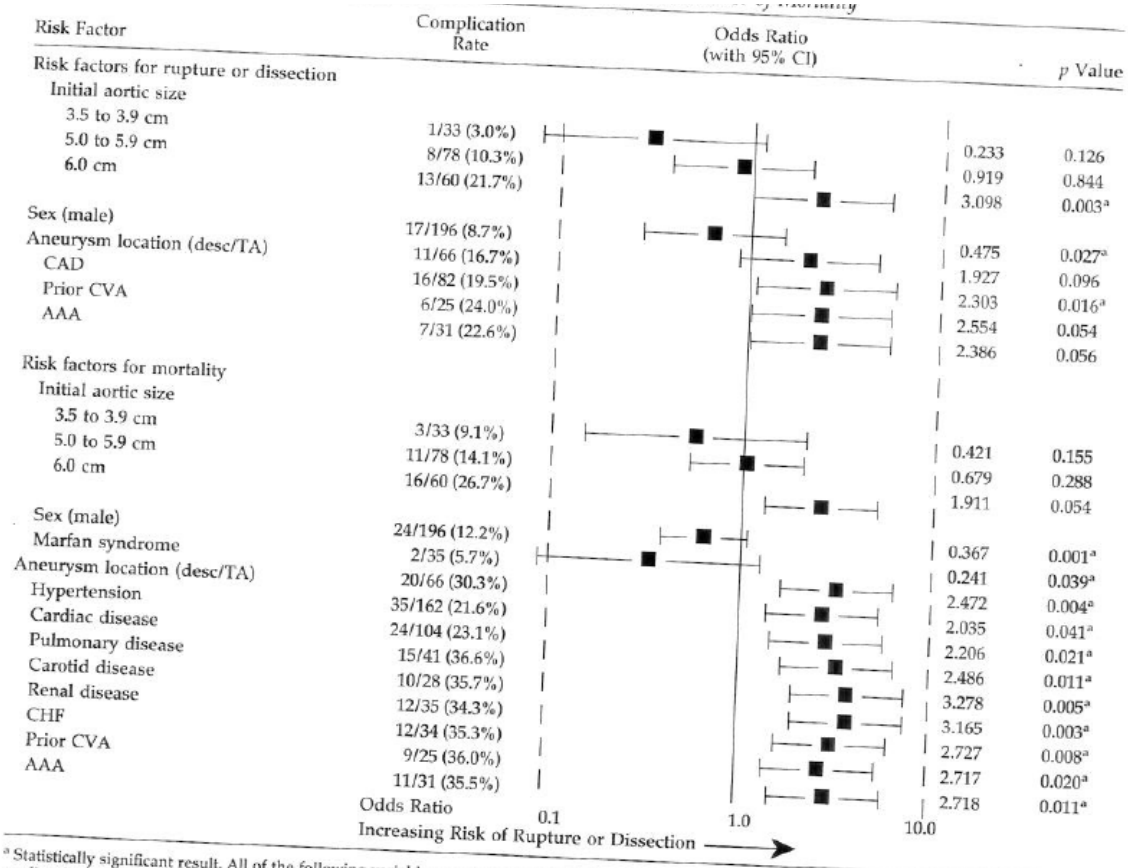


[a] Statistically significant result. All of the following variables were analyzed: initial aortic size, sex, Marfan syndrome, aneurysm location, hypertension, cardiac disease, tobacco history, pulmonary disease, carotid disease, renal disease, coronary artery disease (CAD), congestive heart failure, prior cerebrovascular accident, and history of abdominal aortic aneurysm (AAA). Only results for initial aortic size and those where $p < 0.10$ are shown. Bars on graph indicate 95% confidence intervals (CI), odds ratios cannot be calculated when the incidence of disease is zero.

desc/TA = descending or thoracoabdominal aorta.

Table G-79. Univariate Analysis of Risk Factors Predictive of Rupture or Dissection or of Mortality

Risk Factor	Complication Rate	Odds Ratio (with 95% CI)		p Value
Risk factors for rupture or dissection				
Initial aortic size				
3.5 to 3.9 cm	1/33 (3.0%)		0.233	0.126
5.0 to 5.9 cm	8/78 (10.3%)		0.919	0.844
6.0 cm	13/60 (21.7%)		3.098	0.003[a]
Sex (male)	17/196 (8.7%)		0.475	0.027[a]
Aneurysm location (desc/TA)	11/66 (16.7%)		1.927	0.096
CAD	16/82 (19.5%)		2.303	0.016[a]
Prior CVA	6/25 (24.0%)		2.554	0.054
AAA	7/31 (22.6%)		2.386	0.056
Risk factors for mortality				
Initial aortic size				
3.5 to 3.9 cm	3/33 (9.1%)		0.421	0.155
5.0 to 5.9 cm	11/78 (14.1%)		0.679	0.288
6.0 cm	16/60 (26.7%)		1.911	0.054
Sex (male)	24/196 (12.2%)		0.367	0.001[a]
Marfan syndrome	2/35 (5.7%)		0.241	0.039[a]
Aneurysm location (desc/TA)	20/66 (30.3%)		2.472	0.004[a]
Hypertension	35/162 (21.6%)		2.035	0.041[a]
Cardiac disease	24/104 (23.1%)		2.206	0.021[a]
Pulmonary disease	15/41 (36.6%)		2.486	0.011[a]
Carotid disease	10/28 (35.7%)		3.278	0.005[a]
Renal disease	12/35 (34.3%)		3.165	0.003[a]
CHF	12/34 (35.3%)		2.727	0.008[a]
Prior CVA	9/25 (36.0%)		2.717	0.020[a]
AAA	11/31 (35.5%)		2.718	0.011[a]



[a] Statistically significant result. All of the following variables were analyzed: initial aortic size, sex, Marfan syndrome, aneurysm location, hypertension, cardiac disease, tobacco history, pulmonary disease, carotid disease, renal disease, coronary artery disease (CAD) congestive heart failure (CHE), prior cerebrovascular accident (CVA), and history of abdominal aortic aneurysm (AAA). Only results for initial aortic size and those where $p < 0.10$ are shown. Bars on graph indicate 95% confidence intervals (CI), odds ratios cannot be calculated when the incidence of disease is zero. desc/TA = descending or thoracoabdominal aorta.

Table G-80. Logistic Regression Analysis of Factors Predicting Rupture or Acute Dissection (Dependent Variables)[a]

Regression Analysis Variable	Variable estimate	Standard error	p Value	Odds Ratio[c]
Intercept term	-2.4296	0.4376	0.0001	
Aortic size				
5.0 to 5.9 cm	0.9120	0.5448	0.0941	2.498 (0.856-7.241)
≥ 6cm[d]	1.6538[d]	0.5285	0.0018[d]	5.277[d] (1.855- 14.727)
Gender (male)	-1.0792[d]	0.4490	0.0162[d]	0.340[d] (0.141-0.819)
Cerebrovascular Crash	1.0683	0.5747	0.0630	2.911 (0.944-8.978)
Marfan disease	1.2995[d]	0.6165	0.0350[d]	3.668[d] (1.096-12.278)

[a] This variable equals 1 if the patient incurred a rupture or acute dissection and 0 otherwise. [b] Criteria for assessing model fit: -2 Log L. intercept only, 166.057; intercept and covariates, 145.359; chi-square for covariates, 20.698 with five degrees of freedom (p = 0.0009). [c] 95% confidence intervals on odds ratios are given in parentheses. [d] Statistically significant at 5% level.

Table G-81. Proportional Hazards Regression of Factors Predicting Increased Rates of Rupture or Dissection [a]

Regression Analysis Variable	Variable estimate	Standard error	p Value	Odds Ratio[c]
Size ≥ 6.0 cm [d]	1.101374[d]	0.38774	0.0045[d]	3.008 (1.407-6.432)
CVA[e]	1.041497[b]	0.46201	0.0242[c]	2.833[e] (1.146-7.008)

[a] This variable equals 1 if the patient incurred a rupture and 0 otherwise. [b] Criteria for assessing model fit: -2 Log L; Without covariates, 264.883; with covariates, 253.401; chi-square for covariates.11.482 with two degrees of freedom (p = 0.0032) [c] 95% confidence intervals on odds ratios are given in parentheses.

[d] Statistically significant at 0.5% level. [e] Statistically significant at the 5% level.

Table G-82. Proportional Hazards Regression of Factors Predicting Increased Rates of Rupture [a]

Regression Analysis Variable	Conservative Model Variable Estimate	Entry at p <0.05[b]		
		Standard Error	p Value	Odds Ratio[c]
Initial aortic size				
5.0- 5.9 cm	2.400770[e]	1.12039	0.0321[e]	11.032[e] (1.277- 99.156)
≥ 6.0 cm[d]	3.294935[d]	1.08300	0.0023[d]	26.976[d] (3.229- 225.334)

[a] This variable equals 1 if the patient incurred a rupture and 0 otherwise. [b] Criteria for assessing model fit, -Log L, without covariates, 11.877; with covariates, 103.063; chi-square for covariates, 9.814 with two degrees of freedom (p = 0.0074). [c] 95% confidence intervals on odds ratios are given in parentheses.

[d] Statistically significant at the 0.5% level. [e] Statistically significant at the 5% level.

<table>
<tr><td colspan="14">Davis R, Gallo A, Coady M, Tellides G, Botta D, Burke B, Coe M, Kopf G, Elefteriades J. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 2006; 81: 169-77</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="6">5</td></tr>
<tr><td></td><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="6"></td></tr>
<tr><td>Research Question</td><td colspan="13">To define the impact of body surface area on risk of aortic complications and to assess gender-specific risk</td></tr>
<tr><td>Study Design</td><td colspan="13">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">Patients with thoracic aortic aneurysm followed at Yale University, School of Medicine. Aortic size at least 3.5 cm and age older than 6 years at presentation, absence of congenital aortic malformations</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">Patients presenting with preexisting chronic dissection</td></tr>
<tr><td>Study population characteristics</td><td colspan="12">Variable Value
n 410
Gender M/F 257/153
Additional patient characteristics are noted in Table G-83.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="13">The database of the Yale Center for Thoracic Aortic Disease contained data on patients followed up serially with thoracic aortic aneurysms. Body surface area information was obtained on 410 patients. The investigators calculated a new measure of relative aortic size, the “aortic size index” and examined its ability to predict complications in these patients. Since 2003, height and weight were collected in a prospective fashion; for patients accrued before 2003, height and weight information were obtained from hospital chart review and patient interview. Patients were recruited and followed up between 1985 and 2005. Rupture and dissection were confirmed by at least one of the following: autopsy, operation, death certificates, computer tomography or magnetic resonance imaging.</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">Body surface area (BSA) was calculated using the Dubois and Dubois formula. The interaction between BSA and aortic size was evaluated using the aortic size index (ASI) which was calculated as: ASI = aortic diameter (cm) divided by body surface area (m^2). The method of statistical analysis included chi square test for comparisons of dichotomous risk factors with negative outcomes (rupture, dissection, death); Mantel-Haenszel chi square test for comparisons taking into consideration disease severity; and the Wilcoxon test for comparison of continuous variables with negative outcomes ($p < 0.05$). Logistic regression analysis of the cumulative incidence was used to evaluate the influence of risk factors for rupture or dissection. Product-limit estimates (Kaplan-Meier) were calculated using the LIFETEST procedure of SAS 9.1 for Windows. Yearly rates of complications were calculated as the mean yearly rate over the first 5 years. The Cox regression model was used to identify the most predictive variables.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="12">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 6.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant</td><td colspan="13">Cumulative incidence of major negative events, survival free from these events, and overall long-</td></tr>
</table>

Outcomes Assessed	term survival.
Results	Patients with Marfan syndrome were significantly younger (37.7 years vs. 62.6 and 63.1 years, p <0.0001). Patients with ascending or aortic arch aneurysms were significantly younger at presentation than those with descending or thoracoabdominal aneurysms (60.1 years vs. 69.0 years, p <0.0001); and ascending/arch aneurysms were smaller at initial presentation (5.0 cm vs., 6.0 cm, p <0.0001). Increasing aortic size index was a significant predictor of increasing rates of rupture (p = 0.0014) as well as the combined endpoint of rupture, death, or dissection (p <0.0001). Using aortic size index the patients were stratified into three risk groups: 1) Those with ASI less than 2.75 cm/ / m[2] are at low risk (approximately 4% per year) 2) Those with ASI between 2.75 to 4.24 cm / m[2] are at moderate risk (approximately 8% per year) 3) Those with ASI Above 4.25 cm / m[2]are at high risk (approximately 20% per year) Larger initial ASI predicted worse event-free survival in all categories. Patients with descending or thoracoabdominal aneurysms had higher had higher rupture rates (1- and 5-year rupture free survival 94.9% and 83.0 % vs., 97.2 and 97.2%, p = 0.0009). Five-year survival irrespective of operative repair was only 44% in patients with the largest aortic size index, compared with 94.7% in those with ASI less than 2.00 (p <0.0001). Long–term survival was better for nondissected aortas (5-year survival 73.6% vs. 63.7%, p <0.0001), and for ascending and aortic arch aneurysms compared with those in the descending and thoracoabdominal aorta (76.2% vs. 59.2%, p <0.0001). (Table G-84, Table G-85, Table G-86, Table G-87)
Authors' Comments	Thoracic aortic aneurysm is a lethal disease with relative aortic size more important than absolute aortic size in predicting complications. A novel measurement of relative aortic size allows for the stratification of patients into three levels of risk, enabling appropriate surgical decision-making. The authors recommended elective operative repair before the patient enters the zone of moderate risk with ASI greater than 2.75 cm/ m^2. Despite the inclusion of BSA in the analysis, multivariate models of endpoints that included dissection still included a protective effect of male gender. This finding may indicate that differences other than size account for some of the increased risk in women. Possible contributing factors include changes in the activity of inflammatory mediators in the presence of higher estrogens levels and increased proximal thoracic aortic stiffness in elderly women.

Table G-83. Demographic Data on 401 Patients with Thoracic Aortic Aneurysms

Variable	Number	%	Mean	Median	Range
Gender (male)	257	62.9			
Age at presentation(yrs)			61.9	65.2	8.8 to 92.8
Body surface area (m^2)			1.93	1.94	1.09 to 2.74
Initial aortic size(cm)			5.2	4.9	3.5 to 11.0
3.5 to 4.4 cm	129	31.5			
4.5 to 5.4 cm	155	37.8			
5.5 to 6.4 cm	68	16.6			
6.5 to 7.4 cm	32	7.8			
≥ 7.5 cm	26	6.3			
Final aortic size (cm)			5.7	5.3	3.6 to 12.0
Initial aortic size index (cm / m^2)			2.75	2.50	1.38 to 10.07
Initial aortic size index					
< 2.00 cm/m^2	58	14.2			
2.00 to 2.74 cm/m^2	195	47.6			
2.75 to 3.49 cm/m^2	88	21.5			
3.50 to 4.24 cm/m^2	47	11.5			
4.25 to 4.99 cm/m^2	13	3.2			
>5.00 cm/m^2	9	2.2			
Final aortic size index (cm/m^2)			3.02	2.79	1.52 to 10.07
Radiologic follow-up (months)			31.4	6.3	0.0 to 327.4
Marfan syndrome	23	5.6			
Nonsyndromic family history (n =305)	51	16.9			
Body surface area					
< 2.00 cm^2	239	58.3			
≥ 2.00 cm^2	171	41.7			
Aneurysm location					
Ascending	315	76.8			
Arch	20	4.9			
Descending	41	10.0			
Thoracoabdominal	34	8.3			
Hypertension (n= 356)	238	66.9			
Cardiac disease (n= 349)	119	34.1			
Tobacco use (n = 349)	127	36.4			
Pulmonary disease (n = 353)	83	23.5			
Carotid disease (n = 345)	32	9.3			
Renal disease (n = 352)	27	7.7			
Coronary artery disease (n= 410)	95	23.2			

Congestive heart failure (n= 410)	22	5.4			
Stroke or transient ischemic attacks (n= 410)	23	5.6			
Abdominal aortic aneurysm (n= 410)	38	9.3			

Table G-84. Logistic Regression Analysis of Factors Predicting the Combined Endpoint of Rupture, Dissection, or Death Before Operative Repair

Regression Analysis Variable[b]	Parameter Estimate	Standard Error	*p* Value	Odds Ratio[c]
Intercept term	−2.0435	0.3118	<0.0001	
Aortic size index				
< 2.00 cm/m^2	0.4508	0.4567	0.3235	1.570 (0.641 to 3.841)
2.75 to 3.49 cm/m^2	0.6996	0.3686	0.0577	2.013 (0.977 to 4.146)
3.50 to 4.24 cm/m^2	0.1075	0.5087	0.8327	1.113 (0.411 to 3.018)
4.25 to 4.99 cm/m^2	1.2971	0.6616	0.0499[d]	3.659[d] (1.000 to 13.381)
≥ 5.00 cm/m^2	1.6395	0.7455	0.0279[d]	5.153[d] (1.195 to 22.213)
Aneurysm location (desc/TA)	0.5761	0.3544	0.1040	1.779 (0.888 to 3.564)
Sex (male)	−0.4374	0.3053	0.1519	0.646 (0.355 to 1.175)
History of abdominal aortic aneurysm	0.5669	0.4340	0.1914	1.763 (0.753 to 4.127)

[a] This variable equals 1 if the patient incurred a rupture, dissected, or died before operative repair and 0 otherwise. [b] Variables removed from model in backward fashion, aortic sie index was. Criteria for assessing model fit: −2 Log L: intercept only, 348.351; intercept and covariates: 324.465; χ^2 for covariates (likelihood) ratio): 23,8864 with 8 DF ($p = 0.0024$). [c] 95% confidence intervals on odds ratios are given in parentheses. Odds ratios for aortic size index are given in relation to aneurysms with size index 2.00 to 2.74. [d] Statistically significant at $p < 0.05$ level.

desc/TA = descending or thoracoabdominal.

Table G-85. Proportional Hazards Regression of Factors Predicting Rupture or Dissection

Regression Analysis Variable[b]	Parameter Estimate	Standard Error	*p* Value	Hazard Ratio[c]
Initial aortic size index				
< 2.00 cm/m^2	0.61558	0.46582	0.1863	1.851 (0.743 to 4.612)
2.75 to 3.49 cm/m^2	0.77014	0.37995	0.0427[d]	2.160[d] (1.025 to 4.549)
3.50 to 4.24 cm/m^2	0.38646	0.48015	0.4209	1.472 (0.574 to 3.772)
4.25 to 5.00 cm/m^2	1.46162	0.57268	0.0107[d]	4.313[d] (1.404 to 13.251)
≥ 5.00 cm/m^2	1.23764	0.64803	0.0562	3.447 (0.968 to 12.277)
Aneurysm location (desc/TA)	0.71542	0.31512	0.0232[d]	2.045[d] (1.103 to 3.793)
Age (yrs)	0.01488	0.01014	0.1422	1.015 (0.995 to 1.035)

[a] This variable equals 1 if the patient incurred a rupture or dissection and 0 otherwise. [b] Variables removed from the model is backward fashion. Criteria for assessing model fit: −2 Log: intercept only: 555.772; intercept and covariates: 531.249; χ^2 for covariates (likelihood ratio): 23.7623 with 6 DF ($p = 0.0013$). [c] 95% confidence intervals on hazard ratios are given in parentheses. Hazard ratios for aortic size index are given in relation to aneurysms with size index of 2.00 to 2.74 cm/m^2. Hazard ratio for age indicates the additional hazard for each additional year in age. [d] Statistically significant at $p < 0.05$ level.

desc/TA = descending or thoracoabdominal.

Table G-86. Proportional Hazards Regression Predicting Rupture

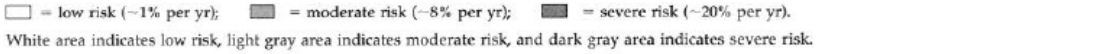
Regression Analysis Variable	Parameter Estimate	Standard Error	*p* Value	Hazard Ratio[c]
Using aortic size index (ASI, cm/m²)[b]				
Initial aortic size index				
< 2.00 cm/m²	1.08300	0.67468	0.1084	2.954 (0.787 to 11.082)
2.75 to 3.49 cm/m²	1.09260	0.60758	0.0721	2.982 (0.906 to 9.810)
3.50 to 4.24 cm/m²	0.50292	0.76178	0.5091	1.654 (0.372 to 7.359)
4.25 to 5.00 cm/m²	2.40316	0.68929	0.0005[d]	11.058[d] (2.864 to 42.698)
≥ 5.00 cm/m²	1.90791	0.86786	0.0279[d]	6.739[d] (1.230 to 36.925)
Aneurysm location (desc/TA)	0.96188	0.45276	0.0336[d]	2.617[d] (1.077 to 36.925)
Using aortic size (cm)[e]				
Initial aortic size				
3.5 to 4.4 cm	−0.41541	0.58127	0.4748	0.660 (0.211 to 2.062)
5.5 to 6.4 cm	0.35126	0.54754	0.5212	1.421 (0.486 to 4.155)
6.5 to 7.4 cm	−0.84354	1.07308	0.4318	0.430 (0.053 to 3.524)
≥ 7.5 cm	1.04947	0.59481	0.0777	2.856 (0.890 to 9.164)
Aneurysm location (desc/TA)	0.84893	0.47299	0.0727	2.337 (0.925 to 5.906)
History of abdominal aortic aneurysm	0.84300	0.50777	0.0969	2.323 (0.859 to 6.285)

[a] This variable equals 1 if the patient incurred a a rupture and 0 otherwise. [b] Variables removed from the model in backward fashion. Criteria for assessing model fit: −2 Log L: intercept only: 265.126; intercept and covariates: 244.199; χ^2 for covariates (likelihood ratio): 20.9261 with 6 DF (p = 0.0019). [c] 95% confidence intervals on hazard ratios are given in parentheses. Hazard ratios for aortic size index are given in relation to aneurysms with size index of 2.300 to 2.74 cm/m². Hazard ratios for aortic size are given in relation to aneurysms with size of 4.5 to 5.5 cm. Hazard ratio for age indicates the additional hazard for each additional year in age. [d] Statistically significant at $p < 0.05$ level. [e] Variables removed from the model in backward fashion. Criteria for assessing mode fit: −2 Log L: intercept only: 265.126; intercept and covariates: 248.882; χ^2 for covariates (likelihood ratio): 16.2433 with 6 DF (p = 0.0125).

desc/TA = descending or thoracoabdominal.

Table G-87. Risk of Complications by Aortic Diameter and Body Surface Area with Aortic Size Given Within Chart

	Aortic Size (cm)									
	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
BSA										
1.30	2.69	3.08	3.46	3.85	4.23	4.62	5.00	5.38	5.77	6.15
1.40	2.50	2.86	3.21	3.57	3.93	4.29	4.64	5.00	5.36	5.71
1.50	2.33	2.67	3.00	3.33	3.67	4.00	4.33	4.67	5.00	5.33
1.60	2.19	2.50	2.80	3.13	3.44	3.75	4.06	4.38	4.69	5.00
1.70	2.05	2.35	2.65	2.94	3.24	3.53	3.82	4.12	4.41	4.71
1.80	1.94	2.22	2.50	2.78	3.06	3.33	3.61	3.89	4.17	4.44
1.90	1.84	2.11	2.37	2.63	2.89	3.16	3.42	3.68	3.95	4.22
2.00	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75	4.00
2.10	1.67	1.90	2.14	2.38	2.62	2.86	3.10	3.33	3.57	3.80
2.20	1.59	1.82	2.05	2.27	2.50	2.72	2.95	3.18	3.41	3.64
2.30	1.52	1.74	1.96	2.17	2.39	2.61	2.83	3.04	3.26	3.48
2.40	1.46	1.67	1.88	2.08	2.29	2.50	2.71	2.92	3.13	3.33
2.50	1.40	1.60	1.80	2.00	2.20	2.40	2.60	2.80	3.00	3.20



White area indicates low risk, light gray area indicates moderate risk, and dark gray area indicates severe risk.

BSA = body surface area.

<table>
<tr><td colspan="15">Elefteriades J. Natural history of thoracic aortic aneurysms: Indications for surgery, and surgical versus nonsurgical risks. Ann Thorac Surg 2002; 74(Suppl): 1877-80</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="5"></td></tr>
<tr><td></td><td colspan="2">√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="5"></td></tr>
<tr><td>Research Question</td><td colspan="14">Natural history of thoracic aortic aneurysms and criteria for surgical intervention</td></tr>
<tr><td>Study Design</td><td colspan="14">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="12">Patients with thoracic aortic aneurysms and dissections followed at Yale University School of Medicine</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="12">NR</td></tr>
<tr><td colspan="2">Study population characteristics</td><td colspan="12">N = 1600 patients with thoracic aortic aneurysms and dissections</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14"></td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Specialized statistical methods were applied to the prospectively accumulated database of 1600 patients with thoracic aortic aneurysms and dissections, which includes 3000 serial imaging studies and 3000 patient years of follow-up.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td colspan="2">Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 6.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Aneurysm growth rate, size of aneurysm at rupture, yearly event rates</td></tr>
<tr><td>Results</td><td colspan="14">The aneurysmal thoracic aorta grows at an average rate of 0.10 cm per year (0.07 for ascending and 0.19 for descending).Hinge points for natural complications of aortic aneurysm (rupture or dissection) were found at 6.0 cm for the ascending aorta and 7.0 cm for the descending. By the time a patient achieved these critical dimensions the likelihood of rupture or dissection was 31% for the ascending and 43% for the descending aorta. A patient with an aorta that has reached 6 cm maximal diameter faces the following yearly rates of devastating adverse events: rupture (3.6%), dissection (3.7%), death (10.8%), rupture, dissection or death (14.1%) (Table G-89). The criteria for intervention in Marfan patients are lower than non-Marfan patients because of the well-known propensity for patients with this disease to dissect at relatively small sizes (Table G-88). Risk of death from aortic surgery for thoracic aortic aneurysm was 2.5% for the ascending aorta and 8% for the descending and thoracoabdominal aortas. The risk of paraplegia is about 8% for descending operations only. These risks are representative of centers with a concentrated experience in aortic diseases.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">In risk /benefit analysis the accumulated data strongly supports a policy of preemptive surgical extirpation of the asymptomatic aneurismal thoracic aorta to prevent rupture and dissection. The authors recommended intervention for the ascending aorta at 5.5 cm and for the descending aorta at 6.5 cm. For Marfan's disease or familial thoracic aortic aneurysm, the authors recommended</td></tr>
</table>

	earlier intervention at 5.0 cm for the ascending and 6.0 cm for the descending aorta. Symptomatic aneurysm must be resected regardless of size. Family members should be evaluated.

Table G-88. Size Criteria for Surgical Intervention for Asymptomatic Thoracic Aortic Aneurysms

	Non-Marfan's	*Marfan's (or familial)*
Ascending	5.5 cm	5.0 cm
Descending	6.5 cm	6.0 cm

Table G-89. Complications Based on Aortic Size

	Aortic Size			
Yearly risk	*>3.5 cm*	*>4 cm*	*>5 cm*	*>6 cm*
Rupture	0.0%	0.3%	1.7%	3.6%
Dissection	2.2%	1.5%	2.5%	3.7%
Death	5.9%	4.6%	4.8%	10.8%
Any of the above	7.2%	5.3%	6.5%	14.1%

<table>
<tr><td colspan="15">Griepp R, Ergin A, Galla J, Lansman S, McCullough J, Nguyen K, Klein J, Spielvogel D. Natural history of descending thoracic and thoracoabdominal aneurysms. Ann Thorac Surg 1999; 67: 1927-30</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="8">5</td></tr>
<tr><td></td><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="8"></td></tr>
<tr><td>Research Question</td><td colspan="14">Assess factors associated with high risk of rupture of aneurysms of the descending thoracic and thoracoabdominal aorta</td></tr>
<tr><td>Study Design</td><td colspan="14">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Patients with chronic dissecting and degenerative aneurysms to the descending thoracic and thoracoabdominal aorta initially managed nonoperatively.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None reported</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">N = 165</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Changes in the aneurysms were followed with three-dimensional reconstructions of computed tomography scans. Risk factors were compared in patients with dissecting and nondissecting aneurysms who experienced rupture, in whom operation was recommended during the course of follow-up, and in those without rupture or operation.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">None reported</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td colspan="13">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td rowspan="2">Score = 4.75</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Factors associated with high risk of rupture</td></tr>
<tr><td>Results</td><td colspan="14">Nondimensional variables associated with an enhanced risk of rupture include age, the presence of chronic obstructive pulmonary disease, and even uncharacteristic continued pain. Results for degenerative aneurysms vs. chronic dissections see Table G-90.
Patients with rupture of dissections had significantly smaller maximal descending thoracic diameters (median 5.4 cm) than patients with rupture of degenerative aneurysms (median 5.8 cm) (p = 0.05). The extent of the aneurysm, as reflected by the maximal abdominal aortic diameter, was a significant risk factor for rupture only in nondissecting aneurysms. Mortality form rupture was significantly higher in patients with chronic dissections than in patients with nondissecting aneurysms: 9/10 vs. 26/34 (p = 0.004). Nearly 20% of patients underwent rupture despite periodic careful surveillance. An overwhelming majority of those who died during the follow-up experienced aortic rupture; 90% of patients with chronic type B dissection and 75% of patients with degenerative aneurysms succumbed to rupture.</td></tr>
<tr><td>Authors'</td><td colspan="14">Almost 20 % of patients followed nonoperatively succumbed to rupture, suggesting that a more</td></tr>
</table>

Comments	aggressive surgical approach toward patients with chronic aneurysms of the descending thoracic and thoracoabdominal aorta is warranted. An individual risk of rupture within 1 year can now be calculated, and patients whose operative risk is lower than their calculated risk should be offered elective surgery.

Table G-90. Comparison of patients with Rupture of Degenerative Aneurysms and Chronic Dissections

	Rupture Data		
	Degenerative Aneurysms	*Chronic Dissections*	*P value*
Rupture rate	26/106	9/50	NS
Rupture deaths	26/34	9/10	0.004
Age (mean, years)	74.9	73.4	0.15
Pain	62%	56%	NS
COPD	35%	67%	NS
Hypertension	69%	78%	NS
Thoracic diameter (cm)	5.8	5.4	0.05
Abdominal diameter (cm)	4.7	3.8	NS

COPD = history of chronic obstructive pulmonary disease

Juvonen T, Ergin A, Galla J. Prospective study of the natural history of thoracic aortic aneurysms. Ann Thorac Surg 1997; 63:1533-45					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
		√			
Research Question	Examine factors predisposing to rupture of descending thoracic and thoracoabdominal aneurysms, including various characteristics of the aneurysm and its pattern of expansion; to better define the risk of aneurysm rupture				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with descending thoracic or thoracoabdominal aortic aneurysm who did not meet standard criteria for immediate surgical intervention and had at least two computed tomography (CT) studies separated by a minimum interval of 3 months. Patients were treated at Mount Sinai Hospital, New York, New York.			
	Exclusion Criteria	Patients with chronic dissection			
	Study population characteristics	Variable Value N 102 90 with descending thoracic 12 with thoracoabdominal aortic aneurysms Age (years) median 72 Gender M/F 59/43 Half of the patients were smokers, and a history of hypertension was found in 2 of every 3 patients. Chronic obstructive pulmonary disease (COPD) was identified in 15 patients. Only 2 patients were identified as having Marfan's disease, and neither of these aneurysms ruptured or required operation. See Table G-91 for complete details			
	Generalizability to CMV drivers	Unclear			
Methods	Patients were monitored by means of clinical examinations and CT scans of the aorta, which were scheduled at 6-month intervals. Follow-up began at the time of each patient's second CT scan, and was terminated either at the time of rupture, the date of the last CT scan preceding an elective operation, or the last date at which the patient was confirmed to be alive without rupture or elective operation, which was July 1, 1996, or later. A medical history geared toward maximizing information about factors likely to contribute to aneurysm rupture was elicited from each patient. Three dimensional computer-generated reconstructions allowed determination of several dimensional parameters, including diameters and cross-sectional areas at the site of maximal dilatation in the descending aorta and in the abdomen.				
Statistical Methods	A piecewise exponential model enabled construction of an equation – based on risks factors such as age, pain, COPD, maximal thoracic and maximal abdominal diameter - allowing calculation of rate of rupture in patients in whom the values of the risk factors are known, and also the probability of rupture in a given individual over a specific time interval. Comparison of demographic and dimensional data between patients with and without aneurysm rupture and between patients who did or did not undergo operation were undertaken using chi square and Wilcoxon tests of significance, as appropriate. Significant risk factors associated with rupture were identified by multivariate regression analysis using the piecewise exponential model, and estimates obtained of				

<table>
<tr><td></td><td colspan="14">corresponding coefficients. All calculations were implemented with SAS program on a VAX computer.</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td rowspan="2">Internal Validity</td><td colspan="14">Revised Newcastle- Ottawa Quality Assessment Scale for cohort studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Score = 6.75</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td>Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Risk factors for rupture of thoracic or thoracoabdominal aortic aneurysm</td></tr>
<tr><td>Results</td><td colspan="14">Of the 114 patients, 8 died of causes unrelated to the aneurysm, 26 died of rupture, 20 met previously determined criteria for operation, and 60 survived without operation or rupture. Four patients who only had two CT scans before operation were excluded from all but the data on patients who underwent operation, because whether or not their aneurysm would have ruptured after their last CT scan could not be known. Multivariate regression analysis identified maximal diameter in the descending and In the abdominal aorta as independent risk factors for rupture, as well as older age, the presence of even uncharacteristic pain, and a history of COPD
(Table G-95). The best equation to estimate rate of rupture, γ, after a CT scan is: Ln γ = -21.055 + 0.093(age) + 0.841 (pain) + 18.22 (COPD) + 0.643 (descending diameter, cm) + 0.405 (abdominal diameter, cm) Where pain and COPD = 1 if present and 0 if absent or not reported, and age refers to the time of the most recent scan. Probability of rupture within 1 year = 1 – e (- I [365])</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The authors recommended operation when the calculated risk of rupture within 1 year exceeds the anticipated mortality of elective operation, rather than relying on general operative guidelines based almost exclusively on aneurysm size.</td></tr>
</table>

Table G-91. Demographic Data of 102 Patients with Chronic Descending TAA

Variable	*n*	*%*	*Median*	*Range*
Gender (male)	59	57.8		
Age (y)			72	40 - 88
Pain	40	39.2		
COPD	15	14.7		
Smoking	55	53.9		
Hypertension	68	66.7		

Diabetes	9	8.8		
% FEV_1 predicted			68	60 - 81

N = 44; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second

Table G-92. Dimensional Measurements in 102 Patients with Chronic Descending TAA

	CT at Entry		Last CT	
Measurement	**Median**	**Range**	**Median**	**Range**
Descending diameter (cm)	4.9	2.5–8.2	5.2	2.5–8.2
Abdominal diameter (cm)	3.8	2.5–7.4	4.4	2.2–8.2
Descending cross-sectional area (cm^2)	24.7	5.2–69.8	29.7	5.2–86.1
Abdominal cross-sectional area (cm^2)	14.1	5.4–50.7	17.1	4.1–63.4
Descending volume (cm^3)	238	49–824	258	66–824
Abdominal volume (cm^3)[a]	90	6–378	114	11–520
Descending circumference (cm)	18.4	8.2–33.0	20.1	8.2–36.8
Abdominal circumference (cm)	13.6	8.4–25.7	15.0	7.4–29.8
Thoracoabdominal surface area (cm^2)	217	76–452	221	76–484
Tortuosity index	1.29	1.11–2.22	1.30	1.11–2.40
Change/year[b]				
Descending diameter (cm)	0.27	0–71.8	0.26	0–9.58
Abdominal diameter (cm)	0.01	0–18.6	0.15	0–23.3
Descending cross-sectional area (cm^2)	2.97	0–1177.8	2.69	0–68.6

[a] Number of slices varies. [b] Annualized change from preceding CT scan.

CT = computed tomography.

Table G-93. Demographic Data in Patients with and without Rupture of Descending TAA

	Unruptured(n = 60)				Ruptured (n = 26)				
Variables	**n**	**%**	**Median**	**Range**	**n**	**%**	**Median**	**Range**	**p Value[a]**
Gender (male)	37	61.7			9	34.6			0.02
Age (y)			71	40-88			74	63-84	0.04[b]
Pain	21	35.0			16	61.5			0.02
COPD	5	8.3			9	34.6			0.002
Smoking	34	56.7			15	57.7			0.93
Hypertension	37	61.7			18	69.2			0.5
Diabetes	6	10.0			2	7.7			0.73
% FEV_1 predicted	31		68	60-80	7		70	63-81	0.46[b]

[a] By chi-square test except [b] Wilcoxon test

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second

Table G-94. Dimensional Measurements in Patients with and without Rupture of Descending TAA

(n= 26)	Unruptured (n=60)			Ruptured	
Measurement	**Median**	**Range**	**Median**	**Range**	**P Value**
Last CT					
Descending diameter (cm)	4.8	2.7-8.1	5.8	3.6-8.2	0.0001
Abdominal diameter (cm)	4.2	2.2-6.2	4.5	3.0-8.2	0.12
Descending cross-sectional area (cm^2)	24.6	7.0-59.6	38.8	14.2-86.1	0.0001
Abdominal cross-sectional area (cm^2)	16.6	4.1-36.2	20.4	8.1-63.4	0.06
Descending volume(cm^3)	231	66-643	326	138-764	0.0001
Abdominal volume(cm^3)[a]	105	22-430	128	12-519	0.5
Descending circumference(cm)	18.2	9.6-31.5	23.1	13.7-36.8	0.0001
Abdominal circumference(cm)	14.8	7.4-23.3	16.2	10.2-29.8	0.05
Thoracoabdominal surface area(cm^2)	206	76-484	265	152-426	0.001
Tortuosity index	1.30	1.11-2.40	1.33	1.17-2.22	0.27
Change / year [b]					
Descending diameter(cm)	0.15	0-9.6	0.4	0-5.3	0.14
Abdominal diameter (cm)	0.02	0-23.3	0.6	0-4.6	0.006
Descending cross-sectional area (cm^2)	0.9	0-68.6	5.8	0-50.5	0.05

[a] Number of slices varies.

[b] Annualized change from next-to-last CT scan.

CT = computed tomography

Table G-95. Independent Risk Factors for Rupture of Descending TAA (Multivariate Analysis)

Risk Factor	*p* Value	Relative Rate
Age	0.02	2.6[a]
Pain	0.04	2.3
COPD	0.004	3.6
Descending aortic diameter	0.003	1.9[b]
Abdominal aortic diameter	0.05	1.50[c]

[a] Relative rate increases by a factor of 2.6 for each decade of age. [b] Relative rate increases by a factor of 1.9 for each cm of descending aortic diameter. [c] Relative rate increases by a factor of 1.5 for each cm of abdominal aortic diameter.

COPD = chronic obstructive pulmonary disease.

Table G-96. Comparison of Significance of Different Dimensional Parameters in Multivariate Analysis of Risk of Rupture in Descending TAA

Dimensional Risk Factor	*p* Value
Descending aortic diameter	0.0001
Descending aortic cross-sectional area	0.0001
Thoracoabdominal surface area	0.003
Descending aortic volume	0.002
Tortuosity index	0.67

Table G-97. Indications for Elective Operation in 20 Patients Operated on for Descending TAA

Indication	n	%
Maximum diameter > 7 cm	16	70
Change/year > 1 cm	10	65
Pain	5	20
Cough	1	5

Table G-98. Demographic Data in Patients with and without Elective Operation for Descending TAA

	No Operation (n = 86)				Elective Operation (n = 20)				
Variable	n	%	Median	Range	n	%	Median	Range	*p* Value[a]
Sex (male)	46	53.5			16	80			0.03
Age (y)			72	40–88			70	46–83	0.1[b]
Pain	37	43.0			5	25			0.14
COPD	14	16.3			2	10			0.48
Smoking	49	60.0			10	50			0.57
Hypertension	55	64.0			15	75			0.35
Diabetes	6	9.3			1	5			0.53
% FEV_1 predicted	38		68	60–81	8		67	59–75	0.29[b]

[a] By χ^2 test except [b] Wilcoxon test.

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second.

Study Summary Tables (Key Question 3)

<table>
<tr><td colspan="6">Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: A multicenter, randomized, controlled trial. Circulation 2001; 104:52-57</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td></td><td></td><td>✓</td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="5">Comparison of the effects of permanent dual-chamber cardiac pacing with pharmacological therapy in patients with recurrent vasovagal syncope</td></tr>
<tr><td>Study Design</td><td colspan="5">RCT</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="4">Patients with recurrent vasovagal syncope; age >35 years; ≥3 syncopal spells in preceding 2 years, with last episode within 6 months of enrollment; positive response to tilt-table testing with syncope occurring in association with relative bradycardia</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="4">Patients with other cause of syncope known or suspected; historical, clinical, or laboratory evidence of cardiac, neurological, or metabolic disease; need for concomitant chronic pharmacological treatment for any cause</td></tr>
<tr><td>Study population Characteristics</td><td>Age
Male (n)
Syncopal episodes in clinical history, median
Syncopal episodes in last 6 months, median
Reported prodromes
Mean duration of prodromes (s)
Asystolic response during tilt testing (n)
Mean duration of asystole (s)
Syncope-related trauma (n)
Major syncope-related trauma (n)
N of study</td><td>Pacemaker
61 ± 13
20
8
2
35
51 ± 54
28
16 ± 18
25
7
46</td><td colspan="2">Drug
55 ± 15
18
7
2
40
46 ± 54
28
18 ± 11
17
3
47</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="4">Unclear</td></tr>
<tr><td>Methods</td><td colspan="5">Patients recruited from consecutive subjects referred to one of 14 participating centers for evaluation of unexplained syncope.

Preliminary diagnostic evaluation included: history, physical, full routine laboratory tests, 12-lead ECG, exercise ECG, Doppler echocardiography, 24-hour ECG monitoring, carotid sinus massage, EEG, and duplex scanning of the carotid arteries.

CT scans and MRI of the CNS and cardiac electrophysiology study performed. Trauma defined as major (any fracture, head injury, internal organ damage requiring hospital admission and surgical</td></tr>
</table>

<table>
<tr><td colspan="15">Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: A multicenter, randomized, controlled trial. Circulation 2001; 104:52-57</td></tr>
<tr><td></td><td colspan="14">treatment) and minor (any bruise, cut, or soft tissue injury)

Head-up tilt testing performed with patient in fasting state. Subjects initially tilted for 60 for 30 minutes (control phase). Those without symptoms received 1.25 mg isosorbide dinitrate sublingually and continued to be tilted for another 15 minutes (pharmacological phase). Test was considered positive if syncope occurred in association with hypotension, bradycardia, or both. In case of syncope, procedure was terminated by rapidly lowering the tilt table to the horizontal position. Pacemaker implantation was performed immediately after randomization. RDR parameters were programmed after implantation and before hospital discharge.

Pharmacological therapy was started immediately after randomization at 50mg/daily. Drug was titrated up to full dosage of 100mg/daily within 2 to 3 days.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Intention-to-treat; on-treatment analysis of the primary end point; Kaplan-Meier cumulative risk of recurrence; Students t test;

Chi square</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Score = 8.3</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td></tr>
<tr><td rowspan="2">Category= High</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">First recurrence of syncope during follow-up</td></tr>
<tr><td>Results</td><td colspan="14">Analysis demonstrated a significant effect in favor of permanent cardiac pacing compared with pharmacological treatment.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">DDD pacing with rate-drop response function is more effective than β blockade for the prevention of syncopal recurrences in highly symptomatic vasovagal fainters with relative bradycardia during tilt-induced syncope.</td></tr>
</table>

Table G-99: Baseline Characteristics

	Pacemaker (n=46)	Drug (n=47)
Age, y	61±13	55±15
Male, n (%)	20 (43)	18 (37)
Syncopal episodes in clinical history, median (minimum–maximum)	8 (3–80)	7 (3–130)
Syncopal episodes in last 6 months, median (minimum–maximum)	2 (1–20)	2 (1–12)
Reported prodromes, n (%)	35 (76)	40 (85)
Mean duration of prodromes, s	51±54	46±54
Asystolic response during tilt testing, n (%)	28 (61)	28 (60)
Mean duration of asystole, s	16±18	18±11
Syncope-related trauma, n (%)	25 (55)	17 (36)
Major syncope-related trauma, n (%)	7 (15)	3 (6)

Table G-100: Primary and Secondary Outcome Events in the Study Population

Outcome Event	Pacemaker	Drug	OR (95% CI), Pacemaker/Drug	*P*
Intention-to-treat analysis				
Patients in analysis, n	46	47		
Syncopal recurrence, n (%)	2 (4.3)	12 (25.5)	0.133 (0.028–0.632)	0.004
Median time to first recurrence (interquartile range), d	390 (360–420)	135 (15–250)		
Follow-up, y	34.4	37.2		
Rate per year	0.06	0.32		
On-treatment analysis				
Patients in analysis, n	45	46		
Syncopal recurrence, n (%)	2 (4.4)	12 (26.1)	0.132 (0.028–0.629)	0.004
Median time to first recurrence (interquartile range), d	390 (360–420)	135 (15–250)		
Follow-up, y	32.04	35.3		
Rate per year	0.05	0.32		

<table>
<tr><td colspan="15">Connolly S, Sheldon R, Roberts R, Gent M. The North American Vasovagal Pacemaker Study (VPS): A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. JACC 1999; 33 (1): 16-20</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td></td><td></td><td>✓</td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="5">Evaluation of pacemaker therapy for severe recurrent vasovagal syncope</td></tr>
<tr><td>Study Design</td><td colspan="5">RCT</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="4">Minimum of 6 syncopal spells; positive tilt-table test with syncope or presyncope and with relative bradycardia</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="4">Other causes of loss of consciousness such as ventricular tachycardia, complete heart block, postural hypotension, hypersensitive carotid sinus syndrome or seizures; important coronary, myocardial, or conduction abnormality; previous pacemaker therapy; contraindication to insertion of a permanent pacemaker, or major chronic non-cardiovascular disease</td></tr>
<tr><td>Study population Characteristics</td><td colspan="4">See Table G-101</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="4">Unclear</td></tr>
<tr><td>Methods</td><td colspan="5">Pilot study of 60 patients initiated. Pacemaker implanted in 26 of 27 patients randomized to pacemaker group (1 refused). None of the no-pacemaker group received a pacemaker prior to experiencing an episode of recurrent syncope. All patients initially programmed into the dual-chamber pacing mode with a minimum rate of 60/min, with the RDR function programmed on.

All patients instructed to keep a daily diary of presyncopal episodes, including grading of syncopal and presyncopal symptoms.

Patient interviewed within 1 week of event to determine whether it was an outcome event. Patients seen every 2 months by study nurses. At planned first formal analysis of efficacy of the pilot study, an unanticipated large treatment effect was observed which fulfilled the prespecified criteria for early termination of the study.</td></tr>
<tr><td>Statistical Methods</td><td colspan="5">Kaplan-Meier cumulative risk of syncope over time; Mantel-Haenszel test for survival curves; Cox proportional hazards model</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td rowspan="2">Internal Validity
Score = 7.0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Category= Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="5">First recurrence of syncope</td></tr>
<tr><td>Results</td><td colspan="5">Marked reduction in post randomization risk of syncope in pacemaker patients (RR reduction 85.4%, CI 59.7% - 94.7%, p = 0.000022).</td></tr>
<tr><td>Authors'</td><td colspan="5">Dual-chamber pacing with rate-drop response reduces the likelihood of syncope in patients with</td></tr>
</table>

Connolly S, Sheldon R, Roberts R, Gent M. The North American Vasovagal Pacemaker Study (VPS): A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. JACC 1999; 33 (1): 16-20	
Comments	recurrent vasovagal syncope

Table G-101: Baseline Characteristics

Feature	No-Pacemaker Group	Pacemaker Group
Number of patients	27	27
Mean age ± SD	40 ± 18	46 ± 18
Female (%)	19 (70)	0
Non-insulin dependent diabetes (%)	2 (7)	0
Hypertension on therapy (%)	3 (11)	4 (15)
Chronic lung disease (%)	1 (4)	2 (7)
Syncope episodes lifetime, median (IQR)	35 (20 – 100)	14 (8-35)
Syncope episodes last year, median (IQR)	6 (3-40)	3 (2-12)
Mean days from most recent syncope episode to randomization (±SD)	63 ± 130	92 ±126
Prior therapy for syncope		
Beta-blocker (%)	11 (41)	12 (44)
Disopyramide (%)	3 (11)	3 (11)
Fludrocortisone (%)	1 (4)	2 (7)
Baseline tilt table test		
Syncope induced (%)	17 (63)	20 (74)
Lowest heart rate <60 bpm, or longest RR>1000 ms	17 (63)	20 (74)
Lowest heart rate < 40 bpm, or longest RR >1500 ms	7 (26)	5 (19)

Connolly S, Sheldon R, Thorpe K, Robert R, Ellenbogen K, Wilkoff B, Morillo C, Gent M. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II) a randomized trial. JAMA 2003; 289:														
Key Questions Addressed	1	2	3	4	5	6								
			✓											
Research Question	To determine if pacing therapy reduces the risk of syncope in patients with vasovagal syncope													
Study Design	RCT													
Population	**Inclusion Criteria**	Patients aged 19 years or older with history of recurrent syncope with at least 6 episodes of syncope in their lifetime, or at least 3 episodes in the 2 years prior to enrollment; positive head-up tilt table result with a heart rate x blood pressure product of <6,000/min. x Hg												
	Exclusion Criteria	Any other cause of syncope present; important valvular, coronary artery, or myocardial disease present; electrocardiographic abnormality; major non cardiovascular disease												
	Study population Characteristics	See Table G-102												
	Generalizability to CMV drivers	Unclear												
Methods	Study population was made up of outpatients referred to syncope specialists at 15 centers. Patients were randomized centrally via the telephone after dual-chamber pacemaker implantation. All patients randomized to ODO group received ODO programming. 44 of 46 patients in the DDD group were randomized to DDD, and 2 received dual-chamber inhibited pacing. Rate drop response was activated initially in all DDD patients.													
Statistical Methods	Log-rank test to compare cumulative risk of syncope													
Quality Assessment	**Internal Validity**	1	2	3	4	5	6	7	8	9	10	11	12	13
	Score = 9.2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Category= High	14	15	16	17	18	19	20	21	22	23	24	25	
		N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	
Relevant Outcomes Assessed	Time to first recurrence of syncope													
Results	Pacing therapy did not reduce the risk of recurrent syncope in patients with vasovagal syncope.													
Authors' Comments	Pacing therapy did not reduce the risk of recurrent syncope in patients with vasovagal syncope. Because of the weak evidence of efficacy with pacemaker therapy and the risk of complications, pacemaker therapy should not be recommended as first-line therapy for patients with recurrent vasovagal syncope.													

Table G-102: Baseline Characteristics

		No (%) of Patients Receiving Treatment*	
Characteristic		**Only Sensing, without pacing (ODO) n=52**	**Dual-Chamber Pacing (DDD) (n=48)**
Men		27 (51.9)	13 (27.1)
Age, mean (SD), years		47.8 (17.7)	50.8 (17.6)
Syncope events, median (IQR)	Total events	20 (8-50)	15 (8-50)
	Events in past year	4 (3-12)	4 (2-15)
	Months since most recent event	1 (0-4)	1 (0-4)
Presyncope episodes, median (IQR)	Last month	6 (1-20)	5 (0-20)
	Last 12 months	24 (5-100)	30 (4-112)
Tilt table test	Duration of test, mean (SD)	29.9 (32.2)	30.4 (23.2)
	Syncope occurred	31 (59.6)	34 (70.8)
	Isoproterenol used	29 (55.6)	21 (43.8)
	Presyncope	40 (76.9)	34 (70.8)
	Lowest systolic blood pressure, mean (SD)	62.6 (27.3)	62.7 (23.3)
	Lowest heart rate, mean (SD)	53.1 (27.8)	56.3 (26.0)
	Lowest heart rate, beats/min < 60	29 (55.6)	29 (60.4)
	Lowest heart rate, beats/min < 40	12 (23.1)	7 (14.6)
Medical history	Diabetes mellitus	4 (8)	4 (8)
	Cardiac disease	5 (10)	5 (10)
	Hypertension (receiving treatment)	12 (23)	13 (27)
	Chronic lung disease	7 (14)	5 (10)
	Other disease	14 (27)	10 (21)
Prior therapy for syncope	Beta-blocker	25 (48)	23 (48)
	Fludrocortisone	10 (19)	9 (19)
	Disopyramide	5 (10)	3 (6)
	Phenylephrine	0	2 (4)
	Selective serotonin reuptake inhibitor	12 (23)	6 (13)
Prior consequences of syncope	Motor vehicle crash	10 (20)	2 (4)
	Driving restrictions	21 (42)	19 (41)
	Bone fracture	6 (12)	4 (9)
	Number/total of those	14/34 (41)	9/29 (31)

		No (%) of Patients Receiving Treatment*	
Characteristic		**Only Sensing, without pacing (ODO) n=52**	**Dual-Chamber Pacing (DDD) (n=48)**
	employed with >15 days of work missed in past year		

*Values expressed as number (percentage) unless otherwise noted

<table>
<tr><td colspan="7">Raviele A, Giada F, Menozzi G, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The Vasovagal Syncope and Pacing Trial
(SYNPACE) European Heart Journal 2004; 25: 1741-48</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td></td><td></td><td>✓</td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="6">Effect of pacing therapy on risk of syncope relapse</td></tr>
<tr><td>Study Design</td><td colspan="6">RCT</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="5">Patients 18 years or older with frequently recurring syncope; positive head-up tilt testing with asystolic or mixed response; a minimum of 6 syncopal episodes in the patient's lifetime, with the last no more than 6 months before enrollment; a minimum of 1 recurrence within 12 months following positive head-up tilt testing</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="5">Patients with any other cause of syncope after a complete work-up; non-vasovagal syncope; syncope due to hypersensitivity of the carotid sinus; recent <6 months) acute myocardial infarction; severe heart failure; abnormalities of cardiac conduction system with possible indication for pacing; chronic severe non-cardiac diseases; already have a pacemaker; pregnancy</td></tr>
<tr><td>Study population Characteristics</td><td colspan="3">See Table G-103
N = 29 (10 males, 19 females)
Mean age of total population
PM On: 52. ± 19
PM Off: 54 ± 18
Cardiovascular Disorders
PM On: 37%
PM Off:38%
Hypertension on therapy (n)
PM On: 3
PM Off :2
Mitral Valve Prolapse (n)
PM On: 3
PM Off: 3
Syncope Episodes Lifetime (n)
PM On: 14
PM Off: 10
Syncope Episodes last 6 months (n)
PM On: 4
PM Off: 2</td><td colspan="2">Duration of symptoms (years)
PM On: 6
PM Off:12
Pre-syncope episodes lifetime (n)
PM On:3
PM Off:2
Major syncope-related trauma (n)
PM On: 4
PM Off:5
Prior ineffective drugs for syncope (n)
PM On: 1.4
PM Off: 1.5
Time from last syncope to randomization (days)
PM On: 17
PM Off: 21</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="6">Patients, investigators, and nurses were unaware of the randomization applied. Randomization was centralized and based on two tables (group 1 and group 2). Patients were divided into two groups on the basis of their heart rate behavior during tilt-induced syncope: Group 1: asystolic response, development of asystole >3 s; Group 2: mixed response, development of bradycardia <60 bpm,</td></tr>
</table>

<table>
<tr><td></td><td colspan="14">without asystole >3 s. As standard therapy for recurrent vasovagal syncope resistant to drug treatment, all patients from both groups underwent implantation of a dual-chamber pacemaker with rate drop response (RDR) function and related diagnostics.

At implantation, pacemakers were centrally randomized to pacemaker ON in DDD mode, with rate drop response RDR or pacemaker OFF with ODO mode. Double-blind randomization to pacemaker ON or pacemaker OFF was clinically followed up until the first recurrence of syncope or the end of the follow-up period (at least 12 months). Pacemaker ON: DDD-RDR mode (lower rate 60 bpm, long AV delay, AV hysteresis ON, rate drop parameters with detention hysteresis 200-400 ms, three confirmation beats, intervention rate 100 bpm, and spontaneous rhythm recovery ON. Patients were asked to keep a clinical diary specifying the number, severity, and time of syncopal and presyncopal events, the circumstances in which they occurred, and any associated traumas.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Kaplan-Meier curves; Students t; Fisher's exact test; Wilcoxon's test; ANOVA; v^2-test; Cox proportional hazards model</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td>Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Score = 9.6</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">Category= High</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">First recurrence of syncope; rate of syncope</td></tr>
<tr><td>Results</td><td colspan="14">The only variable which significantly predicted syncopal recurrence was number of syncope in the patient's lifetime (Table G-104).</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">A high percentage of patients with recurrent tilt-table induced vasovagal syncope continued to have syncopal relapses despite active cardiac pacing and that this percentage is similar to that observed in patients with inactive pacing.</td></tr>
</table>

Table G-103: Baseline Characteristics

	Total population (n = 29)		Mixed group (n = 14)		Asystolic group (n = 15)	
	PM ON (n = 16)	PM OFF (n = 13)	PM ON (n = 8)	PM OFF (n = 6)	PM ON (n = 8)	PM OFF (n = 7)
Age, years (mean ± SD)	52 ± 19	54 ± 18	53 ± 17	56 ± 9	50 ± 21	52 ± 15
Female gender, n (%)	12 (69)	7 (54)	4 (50)	5 (83)	8 (100)	2 (19)[a]
Cardiovascular disorders, n (%)	6 (37)	5 (38)	3 (37)	3 (50)	3 (37)	2 (29)
Hypertension on therapy, n	3	2	1	1	2	1
Mitral valve prolapse, n	3	3	2	2	1	1
Syncope episodes lifetime, n (median, IQR)	14 (9–30)	10 (6–23)	23 (10–32)	18 (10–105)	12 (8–27)	7 (6–12)
Syncope episodes in the last 6 months, n (median, IQR)	4 (3–6)	2 (1–4)	4 (3–5)	3 (2–12)	4 (2–9)	2 (1–4)
Duration of symptoms, years (median, IQR)	6 (4–25)	12 (3–27)	5 (1–20)	11 (3–33)	18 (5–35)	24 (2–27)
Pre-syncope episodes lifetime, n (median, IQR)	3 (0–10)	2 (0–10)	3 (0–10)	6 (0–10)	3 (0–9)	2 (0–10)
Major syncope-related trauma, n (%)	4 (25)	5 (38)	3 (38)	2 (33)	1 (13)	3 (43)
Prior ineffective drugs for syncope, n (mean ± SD)	1.4 ± 0.8	1.5 ± 1.1	1.3 ± 1.1	1.8 ± 1.3	1.5 ± 0.5	1.1 ± 0.9
Time from last syncope to randomisation, days, (mean ± SD)	17 ± 10	21 ± 15	19 ± 11	17 ± 10	16 ± 9	24 ± 18

IQR: interquartile range; PM: pacemaker; SD: standard deviation.
[a] PM OFF vs PM ON in the Asystolic group: p = 0.01.

Table G-104: Findings

	Total population		Mixed group		Asystolic group	
	PM ON	PM OFF	PM ON	PM OFF	PM ON	PM OFF
Intention-to-treat analysis						
Patients in analysis, *n*	16	13	8	6	8	7
Syncopal recurrence, *n* (%)	8 (50)	5 (38)	4 (50)	3 (50)	4 (50)	2 (29)
Time to first recurrence, days, (median, IQR)	97 (38–144)	20 (4–302)	88 (13–387)	100 (7–505)	97 (50–140)	11 (2–20)
Syncopal rate, *n*/month (mean ± SD)	0.04 ± 0.06	0.08 ± 0.15	0.04 ± 0.06	0.13 ± 0.20	0.05 ± 0.07	0.04 ± 0.09
Pre-syncopal recurrence, *n* (%)	12 (75)	5 (38)	7(87)	2 (33)	5 (62)	3 (43)
Total pre-syncope episodes, *n* (median, IQR)	1 (0–4)	0 (0–4)	1 (0–4)	1 (0–11)	1 (0–4)	0 (0–1)
Follow-up, days (median, IQR)	563 (355–825)	730 (247–785)	562 (385–872)	722 (228–763)	630 (267–745)	780 (255–820)
On-treatment analysis						
Patients in analysis, *n*	17	12	9	5	8	7
Syncopal recurrence, *n* (%)	8 (47)	5 (42)	4 (44)	3 (60)	4 (50)	2 (29)
Time to first recurrence, days, (median, IQR)	97 (38–144)	20 (4–302)	88 (13–387)	100 (7–505)	97(50–140)	11 (2–20)
Syncopal rate, *n*/month (mean ± SD)	0.05 ± 0.06	0.09 ± 0.19	0.04 ± 0.06	0.19 ± 0.27	0.05 ± 0.07	0.04 ± 0.09
Pre-syncopal recurrence, *n* (%)	12 (71)	5 (42)	7 (78)	2 (40)	5 (62)	3 (43)
Total pre-syncope episodes, *n* (median, IQR)	1 (0–4)	0 (0–2)	1 (0–4)	0 (0–6)	1 (0–4)	0 (0–1)
Follow-up, days (median, IQR)	575 (360–800)	745 (244–788)	575 (400–865)	715 (216–767)	630 (267–745)	780 (255–820)

IQR: interquartile range; PM: pacemaker; SD: standard deviation.

Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: Pacemaker vs. no therapy: A multicenter, randomized study. Circulation 2000; 18: 294-299														
Key Questions Addressed	1	2	3	4	5									
			✓											
Research Question	Comparison of implantation of DDI pacemaker with rate hysteresis to no implant in respect to syncopal recurrences in patients with severe cardioinhibitory tilt-positive neurally mediated syncope													
Study Design	RCT													
Population	**Inclusion Criteria**	Neurally mediated syncope; ≥ 3 syncopal episodes in last 2 years with last episode occurring within 6 months of enrollment and with an interval between the first and last episode of >6 months; positive VASIS type 2A or 2B cardioinhibitory response to head-up tilt testing; age >40 years or if <40 years old, proven refractoriness to conventional drug therapy												
	Exclusion Criteria	Syncope other than vasovagal; recent (<6 months) myocardial infarction; severe heart failure; concomitant severe chronic disease (diabetes mellitus, neurological diseases, terminal diseases, and neoplasia)												
	Study population Characteristics	See Table G-105												
	Generalizability to CMV drivers	Unclear												
Methods	Patients were assigned to 1 of 2 study arms by central computer-generated randomization list. Immediately post-randomization Pacemaker patients received a DDI pacemaker with rate hysteresis programmed as follows: DDI, 80 bpm; hysteresis, 45 bpm and AV interval, 150 ms. Immediately post-randomization No- Pacemaker patients received no specific therapy. Any other treatment for syncope was forbidden. Further head-up tilt test was performed within 15 days of enrollment in the patients in both groups. During follow-up, patients were monitored either clinically or by telephone interview.													
Statistical Methods	Intention to treat; odds ratio of the 2-binomial proportions analysis; time to first syncopal analyzed by Kaplan-Meier survival curves, with curves compared by means of log-rank test													
Quality Assessment	**Internal Validity**	1	2	3	4	5	6	7	8	9	10	11	12	13
	Score = 8.8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR
	Category= High	14	15	16	17	18	19	20	21	22	23	24	25	
		NR	NR	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Relevant Outcomes Assessed	First recurrence to syncope													
Results	1 patient in the pacemaker group experienced syncope recurrence compared to 14 patients in the no-pacemaker group. On repeated tilt testing within 15 days of enrollment, positive responses were observed in 59% of pacemaker patients and 61% of no-pacemaker patients (Table G-106).													

Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: Pacemaker vs. no therapy: A multicenter, randomized study. Circulation 2000; 18: 294-299	
Authors' Comments	In a limited, select group of patients with tilt-positive cardioinhibitory syncope, DDI pacing with hysteresis reduced the likelihood of syncope. Benefit of therapy was maintained over the long term. Syncopal recurrence was low even in untreated patients.

Table G-105: Baseline Characteristics

Characteristic	Pacemaker (n=19)	No Pacemaker (n=23)
Age, years	64 ± 11*	56 ± 14*
Male, n (%)	11 (58)	13 (57)
Syncope episodes in lifetime, n, median, (interquartile range)	5 (3-12)	6 (3-10)
Syncope episodes in last 2 years, n, median, (interquartile range)	3 (3-4)	3 (3-4.5)
Duration of symptoms, years, median (interquartile range)	4 (2-14)	5 (2.5-12)
Presyncope n(%)	12 (63)	16 (70)
Presyncope episodes in last 2 years, n, median (interquartile range)	4 (1-10)	6 (5-30)
Trauma secondary to syncope	8 (42)	10 (43)
Previous drug treatment, n(%)	2 (11)	4 (17)
History of suspected vasovagal or situational syncope, n (%)	10 (53)	13 (57)
Associated cardiovascular disorders, n(%)	9 (47)	7 (30)
o Hypertension on therapy, n	4	4
o Atherosclerotic, n	4	3
o Valvular, n	1	1
ECG abnormalities, n (%)	3 (16)	4 (17)
Echocardiographic abnormalities, n (%)	6 (32)	6 (26)
Response to baseline testing		
o Type 2 A, n (%)	8 (42)	8 (35)
o Type 2 B, n (%)	8 (42)	11 (45)
o Type 2 (undefined), n (%)	3 (16)	4 (17)
o Asystolic, n (%)	15 (79)	21 (91)
o Mean asystolic	15.2 ± 12.0	13.0 ± 8.9

*P = 0.05

Table G-106: Findings

Outcome Event	Pacemaker	No Pacemaker	Risk Ratio (95% CI)	*P*
Intention-to-treat analysis				
Patients in analysis, n	19	23		
Syncopal recurrence, n (%)	1 (5)	14 (61)	0.04 (0.005–0.3)	0.0006
Total syncope episodes, n	2	26		
Mean per patient, n	2	1.9±1.2		
Median time to first recurrence, mo (interquartile range)	15	5 (2–20)		
Follow-up, y	72.2	75.9		
Rate per year	0.03	0.34		
On-treatment analysis				
Patients in analysis, n	22	20		
Syncopal recurrence, n (%)	1 (5)	14 (70)	0.02 (0.003–0.2)	0.0001
Total syncope episodes, n	2	24		
Mean per patient, n	2	1.7±0.9		
Median time to first recurrence, mo (interquartile range)	15	5 (2–20)		
Follow-up, y	77.8	54.7		
Rate per year	0.03	0.44		
Acute effect (repeated positive tilt testing), n (%)	10/17 (59)*	11/18 (61)*	0.84 (0.19–4.3)	0.84

*Control tilt testing not performed in 5 and 2 patients in the pacemaker and no-pacemaker groups, respectively, because of patient refusal.

Study Summary Tables (Key Question 4)

<table>
<tr><td colspan="15">Akiyama T, Powell J, Mitchell L, Ehlert F, Baessler C. Resumption of driving after life-threatening ventricular tachyarrhythmia. N Engl J Med 2001;345:391-7</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="3"></td><td colspan="3">✓</td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">Risk of patients driving after life-threatening ventricular tachyarrhythmias in patients treated with antiarrhythmic medication (amiodarone) and implantable cardioverter-defibrillators (ICDs)</td></tr>
<tr><td>Study Design</td><td colspan="14">Survey</td></tr>
<tr><td>USPSTF Level</td><td colspan="14">II-2</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Participants in the AVID trial recruited between June 1, 1993 and April 7, 1977.
(The AVID trial compared antiarrhythmic drug therapy with the implantation of defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997:337:1576-83.)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Subjects not responding to first questionnaire; responded as non-drivers before enrollment in the AVID trial</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Variable — Value
n — 627
Age (years) mean ±SD — 64.5±10.1 years.
Gender M/F — 537/90</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Subjects were asked if they continued to drive, estimate the amount of driving and indicate type of driving (residential roads, rural roads highway driving, etc.). Study patients were also asked questions about possible arrhythmia-related symptoms while they were driving.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Student's t-test; chi-square test or paired-sign test; Cox proportional-hazards model. Statistical significance indicated by a two-tailed P value of less than 0.05.</td></tr>
<tr><td rowspan="6">Quality Assessment</td><td rowspan="2">Internal Validity</td><td colspan="13">Items met : Survey Assessment Tool</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Score = 5.0</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="4">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
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<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Reported symptoms of possible arrhythmia, annual risk of motor vehicle crash</td></tr>
<tr><td>Results</td><td colspan="14">Of 627 study patients, 57 percent resumed driving within 3 months, 78 percent within 6 months, and 88 percent within 12 months after randomization in the AVID trial, despite recommendations of their physicians not to drive. Of 500 patients who reported driving before receiving the first questionnaire, 63 percent reported driving the same amount as the previous year, 34 per cent reported driving less,</td></tr>
</table>

	and 3 percent reported driving more. Patients reporting driving more on residential roads, than rural roads, urban roads or highways (Table G-107). 91% of subjects reported driving at least once per week. 57% reported driving daily. 46% drove less than 50 miles per week and 25 percent were driving more than 100 miles/week. Of the 627 patients, 563 (90 percent) resumed driving. A total of 559 of the patients (99 percent) responded to questions on symptoms of possible arrhythmia (Table G-108). Two percent had lost consciousness while driving, 11 percent reported dizziness or palpitations necessitating stopping the vehicle and 22 percent reported dizziness or palpitations that did not necessitate stopping the vehicle. Of 295 patients who resumed driving after having receive an ICD 8 percent reported receiving a shock while driving - 6 percent received a shock once, 1 percent twice, and 1 percent three times. Fifty of the 559 patients reported having at least 1 motor vehicle crash (9 percent, 95% CI = 6.5-11.3 percent) for total of 55 crashes. Total of 55 crashes during a mean follow-up of 35 months. Crashes were preceded by symptoms of possible arrhythmia in 6 of the 55 cases (11 percent; 95% /cu = 2.5 to 19.7 percent) loss of consciousness in 3 instances, dizziness in 1, palpitations in 1, and both dizziness and palpitations in 1. None of the crashes were preceded by a shock from an ICD. No difference in crash frequency between antiarrhythmic drug therapy group and ICD group (data not shown). 295 in ICD group and 304 on antiarrhythmic drug. No patient died because of an automobile crash. Annual risk of motor vehicle crashes in patient population was 3.4 percent 95% CI (2.5-4.3 percent). Annual risk of motor vehicle crash presumed to be related to arrhythmia was 0.4 percent, 95% CI (0.1-0.7 percent). The year before the index episode of ventricular tachyarrhythmia, the annual rate of motor vehicle crashes was 6.2 percent. Authors also conducted sensitivity analysis assuming various crash rates for patients with missing data. Analysis is summarized in Table G-109. The vast majority of patients who did not respond would have had to have a crash to invalidate the conclusions.

Authors' Comments	The annual 3.4 percent probability of a motor vehicle crash is lower than the 7.1 percent annual probability of a motor vehicle crash for all drivers in the United States based on 1997 data from the National Highway Traffic Safety Administration. The power of this study is limited with respect to the estimation of the probability of events with very low frequency. There was a disparity between frequency of symptoms of possible arrhythmia and consequent motor vehicle crashes, indicating that most patients were able to maintain control of their vehicles. The study is questionnaire-based so it was dependent on the cooperation, understanding, truthfulness and memory of the patients. Observations were also limited to patients who felt well enough to have resumed driving despite recommendations that they not do so. Also, no data on injury or death in persons other than study participants in motor vehicle crashes were obtained. Another limitation is that 11 percent of the patients in the AVID trial died before receiving the first driving questionnaire, which was completed a median of 9 months after enrollment in the trial. No conclusions can be made about this group of patients. Therefore, the study group is a study of patients who lived long enough to complete the first questionnaire. Lowenfal in Letter to the Editor regarding the article remarked that the National Highway Traffic Safety Administration's data covers all crashes, including property damage only, which accounts for two-thirds of all reported crashes. Subjects might not report a property damage only crash (or any crash) because they were advised by their doctors not to drive and were unwilling to give up this privilege.
Reviewers' Comments	Results were not adjusted for mileage. After surviving an episode of ventricular arrhythmia, drivers would be motivated to be more careful, if only because a crash might result in loss of license. This may explain the reduction in the crash rate after the episode of ventricular arrhythmia.

Table G-107: Driving Environments

Frequency of Use	Rural (N=453)	Residential (N=476)	Urban (N=458)	Highway (N=473)
	number of patients (percent)			
Never	81 (18)	3 (1)	40 (9)	68 (14)
Sometimes	254 (56)	189 (40)	264 (58)	295 (62)
Most of the time	73 (16)	193 (41)	110 (24)	79 (17)
All of the time	45 (10)	91 (19)	44 (10)	31 (7)

*Data are for the 500 patients who had resumed driving before receiving the initial questionnaire. Different numbers of patients answered questions about different environments.

Table G-108: Symptoms of Possible Arrhythmia

No. of Events	Syncope (N=557)	Dizziness or Palpitations Necessitating Stopping (N=556)	Dizziness or Palpitations Not Necessitating Stopping (N=554)
	number of patients (percent)		
0	546 (98)	495 (89)	430 (78)
1	7 (1)	27 (5)	43 (8)
2	1 (<1)	12 (2)	21 (4)
>2	3 (1)	22 (4)	60 (11)

*Data are for the 559 patients who reported having resumed driving and who answered questions regarding possible arrhythmia-related symptoms that occurred while they were driving. Different numbers of patients answered questions about different symptoms.

Table G-109: Sensitivity Analysis

Assumed Accident Rate in Subgroup (%)	Resulting Accident Rate for All Patients		
	Patients who did not respond to questionnaire but were thought to be driving (N=65)	Patients who did not answer questions about accidents (N=58)	Both types of patients (N=123)
	percent (95 percent confidence interval)		
0	3.4 (2.5–4.3)	3.4 (2.5–4.3)	3.4 (2.5–4.3)
10	3.4 (2.6–4.3)	3.4 (2.6–4.3)	3.4 (2.6–4.2)
20	3.8 (2.9–4.7)	3.7 (2.9–4.6)	4.1 (3.2–4.9)
30	4.1 (3.2–5.1)	4.1 (3.1–5.0)	4.7 (3.7–5.6)
40	4.5 (3.5–5.5)	4.4 (3.4–5.3)	5.3 (4.3–6.3)
50	4.9 (3.9–5.8)	4.7 (3.7–5.7)	5.9 (4.9–7.0)
60	5.2 (4.2–6.2)	5.0 (4.0–6.1)	6.6 (5.5–7.6)
70	5.6 (4.5–6.6)	5.4 (4.3–6.4)	7.2 (6.0–8.3)
80	5.9 (4.8–7.0)	5.7 (4.6–6.8)	7.8 (6.6–9.0)
90	6.3 (5.2–7.4)	6.0 (4.9–7.1)	8.4 (7.2–9.7)
100	6.7 (5.5–7.8)	6.3 (5.2–7.5)	9.1 (7.8–10.3)

Conti J, Woodard D, Tucker K. Modification of patient driving behavior after implantation of a cardioverter defibrillator. PACE 1997;20: 2200-2204														
Key Questions Addressed	1	2	3	4	5									
				✓										
Research Question	Rate of ICD discharge during driving													
Study Design	Descriptive, non-experimental													
Population	**Inclusion Criteria**	Patients who received an ICD at the University of Florida												
	Exclusion Criteria	None reported												
	Study population Characteristics	Study population characteristics are presented in Table G-111												
	Generalizability to CMV drivers	Unclear												
Methods	Standardized questionnaire to ascertain driving behavior, compliance with restrictions, and occurrence of motor vehicle crashes following ICD implantation. Interviews were conducted by a single interviewer, a nurse trained in clinical electrophysiology. Questionnaire is presented in Table G-110. Patients were divided into two groups: Group I received a shock, Group II did not.													
Statistical Methods	All data reported as mean ± SD. Student's paired *t*-test was used for comparison between the two groups.													
Quality Assessment	**Internal Validity**	1	2	3	4	5	6	7	8	9	10	11	12	13
	Score = 5.0	NR	NR	NR	NR	Y	Y	NR	NR	Y	Y			
	Category= Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Device discharge during driving, daily driving mileage													
Results	In this group of patients, in which 73 returned to driving after the implantation of an ICD, there were no device discharges since implant. Daily driving mileage was 20.5±27 miles in Group I and 8.3±9.7 in Group II.													
Authors' Comments	Patients were found to change driving habits, specifically by not driving on highways, driving shorter distances, driving with someone, or abstaining from driving. These decisions had little to do with whether or not they received a shock.													
Reviewers' Comments	The time since implant of the ICD was relatively short , 6±1.3 months for Group I and 4±1.5 for Group II, while the average wait to resume driving was 13.8±18.3 months in Group I and 12.3±13.9 in Group II.													

Table G-110: Patient Questionnaire

1. When was your ICD implanted?
2. Has your device fired since implantation?
3. Have you had symptoms prior to the device firing?
   palpitations____ lightheadedness____
   loss of consciousness____ heart racing____ other
4. Have you driven a motor vehicle since the device was implanted?
5. How soon after implantation did you start driving?
6. Did your doctor tell you it was all right to drive? If so, what were the conditions?
7. Has your device ever fired while you were driving? If yes, please specify the number of times and comment.
8. Have you ever been in an accident because of your device firing?
9. Had you ever been in an accident because of your arrhythmia, before you received your device?
10. If you have been in an accident, either with or without the device, who was injured?
    ____yourself ____your passengers(s)
    ____other driver ____other passenger(s)
11. Did you follow your doctor's advice about driving?
12. Approximately how far do you drive each day?
13. Have your driving habits changed since implantation of the device, i.e., does someone always drive with you, do you avoid major highways, do you drive shorter distances, etc.?

Table G-111: Demographic Data and Summary of Results of Survey

	Device Discharge Since Implant (Group I)	No Discharge Since Implant (Group II)	P Value
N =	52	30	—
Mean Age	62 ± 11	64 ± 13	NS
Months since implant	6 ± 1.3	4 ± 1.5	0.002
No symptoms prior to ICD discharge	24 (51%)	N/A	—
Returned to driving a vehicle after ICD implantation	47/52 (90%)	26/30 (87%)	NS
Average wait to resume driving	13.8 ± 18.3	12.3 ± 13.9	NS
Device discharge during driving	0	0	NS
MVA secondary to device firing	0	0	NS
Daily driving mileage	20.5 ± 27	8.3 ± 9.7	0.02

ICD = implantable cardioverter defibrillator; MVA = motor vehicle accident.

Craney J, Powers M. Factors related to driving in persons with an implantable cardioverter defibrillator. Progress in Cardiovascular Nursing 1995; 10(3):12-17														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
							✓							
Research Question	Patients risk to resume driving post-ICD implantation													
Study Design	Survey													
Population	**Inclusion Criteria**	100 consecutive subjects selected from a list of patients with ICDs implanted at a Mid-Atlantic university-affiliated medical center; had an ICD for a minimum of six months; speak and understand English; had a telephone in their place of residence; not hospitalized at the time of interview												
	Exclusion Criteria	None reported												
	Study population characteristics	See Table G-112 for demographic data.												
	Generalizability to CMV drivers	Unclear												
Procedures	25-item semi-structured questionnaire designed to measure the length of time since ICD implant, whether presently driving, and if so, how far, how often, and under what conditions. Also, information about frequency and type of symptoms experienced during a dysrhythmia was requested, and whether a discharge from the ICD was received in the past year, especially while driving.													
Statistical Methods	Descriptive statistics were used to systematically assess for missing data, marked skewness, and outliers. Descriptive statistics were then used to summarize responses to all questions, thus indicating the demographics of the population, the percentage of subjects driving, and characteristics of their driving habits. Descriptive statistics also indicated the presence of symptoms related to arrhythmia and the percentage of persons who received a shock from their ICD. To determine if relationships exist between the independent variables and driving, Pearson *r* correlations were performed.													
Quality Assessment	**Internal Validity**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Score = 5.0		**NR**	**NR**	**NR**	**NR**	**Y**	**Y**	**NR**	**NR**	**Y**	**NR**			
	Category= Low		**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
Relevant Outcomes Assessed	Percentage of patients continuing to drive; driving habits; symptoms of syncope and number of ICD shocks while driving													
Results	97 patients completed the questionnaire. A partial list of the results is presented in Table G-113. The presence of physical symptoms was not significantly related to the decision to drive. Despite experiencing dizziness, palpitations, lightheadedness, or shortness of breath on a regular basis, subjects chose to drive. Also, there was no significant relationship between receiving a shock from the device in the past year and driving.													

Craney J, Powers M. Factors related to driving in persons with an implantable cardioverter defibrillator. Progress in Cardiovascular Nursing 1995; 10(3):12-17	
Authors' Comments	Many subjects defended their decision to drive by taking precautions to limit driving to off-peak hours, back roads, and daylight hours. The percentage of persons receiving a shock while driving was insignificant and similar to previous published findings. The average age in the authors' population of interest was 66. The authors cited previously published studies and statistics that suggest that 8.3% people aged 65 and older with any disease die in motor vehicle crashes, and that individuals with cardiovascular disease have a 62% higher rate of crashes than other groups, although driver mortality due to ventricular tachycardia was reported to be low.

Table G-112: Demographic Data

	Mean	*Range*
Age	66±9.7 yrs	30 – 84 yrs
Gender	72 (males) 25 (females)	
Time Since Implant	2.2 yrs	6 mos. – 9 years

Table G-113: Partial List of Responses on Driving Questionnaire

Patients who reported driving	74%
Average mileage	60 miles/week
Patients who received a shock while driving	>4%
Patients experiencing dizziness, palpitations and lightheadedness	80%
Patients receiving a shock from their ICD within the past year	43%

<table>
<tr><td colspan="15">Finch N, Sneed N, Leman R, Watson, J. Driving with an internal defibrillator: Legal, ethical, and quality-of-life issues. J Cardiovasc Nurs 1997; 11(2): 58-67</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td></td><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">Repercussion for patients who continue to drive after ICD implantation</td></tr>
<tr><td>Study Design</td><td colspan="14">Survey</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Subjects who had received an ICD implant at the Medical University of South Carolina in Charleston, SC</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">None stated</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">Variable Value
N 105
Age (years) mean 61 years
Gender M/F 79% M

73.3% admitted with syncope, dizziness or sudden cardiac death and subsequently received the ECD.
Mean VEF – 36%. Range of 12% to 75% in 88 of 105 patients.
Second -generation devices – 55 patients
Third-generation devices – 50 patients including several experimental units
Average time from implantation to interview – 21.6 months
Nine patients had second device.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Telephone questionnaire designed by investigators.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">None</td></tr>
<tr><td rowspan="4">Quality Assessment</td><td rowspan="2">Internal Validity
Score = 4.0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>NR</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Category= Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Driving habits; incidence of shocks.</td></tr>
<tr><td>Results</td><td colspan="14">Despite medical advice prohibiting driving 77% of patients resumed driving. Ten stopped driving because of physician's advice. Fear kept four patients from driving and four patients were non-drivers before implantation. Medical problems cited by remaining six patients. Patients waited an</td></tr>
</table>

Finch N, Sneed N, Leman R, Watson, J. Driving with an internal defibrillator: Legal, ethical, and quality-of-life issues. J Cardiovasc Nurs 1997; 11(2): 58-67	
	average of 3.9 months to drive after ICD implant (range 0-24 months). Two patients drove themselves home from the hospital. 49% of patients reported having received at least one shock (range 1-141). 53% had received no shocks Of the 52 patients who reported shocks, 25 (49%) experienced symptoms during the shock episode. In 20 of these patients (80%) symptoms were potentially incapacitating (e.g., Dizziness, 15 (60%), loss of consciousness, 5 (20%). Only three patients were shocked behind the wheel and none of these shocks resulted in crash or injury.
Authors' Comments	Factors that could affect risk of an individual ICD patient include how much driving the patient does and when and where it occurs.

Finch N, Leman R, Kratz J, Gillette, P. Driving safety among patients with automatic implantable cardioverter defibrillators. JAMA 1993; 270:1587-1588					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
				✓	
Research Question	Driving behavior of patients following the placement of an ICD				
Study Design	Survey				
Population	**Inclusion Criteria**	40 consecutive patients who had ICDs implanted at the Medical University of South Carolina			
	Exclusion Criteria				
	Study population characteristics	Males -33; Females -7 Length of time since ICD implant - (1 month to 3 years) Number of patients aware of ICD discharges – 26			
	Generalizability to CMV drivers	Unclear			
Procedures	A questionnaire was developed to ascertain driving behavior in ICD patients. Questionnaire was administered by one interviewer, the cardiology case manager, who coordinated the patient's care during their ICD implantation and followed up the patients in the clinical setting.				
Statistical Methods	None				

Quality Assessment

Internal Validity												
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Score = 4.0	**NR**	**NR**	**NR**	**NR**	**Y**	**NR**	**NR**	**NR**	**Y**	**NR**			
Category= Low	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
	26	**27**	**28**										

Relevant Outcomes Assessed	Questionnaire Components If and when patients began driving postoperatively How much (daily or number of times/week)? Where (locally, in city, or on an interstate highway? Whether they were primary driver in the family If they felt comfortable and safe while driving Whether or not they had contacted their insurance companies and/or their state's department of motor vehicles.
Results	Despite being told not to drive after ICD implantation 28 of 40 patients (70%) had resumed driving (TABLE G-114). One patient drove himself home from the hospital. The majority of those driving did so by 8 months following implantation.
Authors' Comments	Majority of patients with ICDs who are physically able to drive do so despite advice to the contrary. Regarding a published survey of physician management of cardiac patients, "Cardiologists were more likely to place driving restrictions on their patients with ICDs than on patients treated with medications. They may reason that drugs may prevent arrhythmias while the ICD does not".

TABLE G-114: PARTIAL RESULTS OF QUESTIONNAIRE

Item	Response
Resumed driving	28 (70%)
Time from hospital discharge to resumption of driving	As early as 2 weeks (one patient even drove home from hospital. Majority were driving by 8 months.
Patient is primary driver in household	11 (40%)
Drove on a daily basis	14 (50%)
Drove on major highways	21 (75%)
Drove only locally	7 (25%)
Experienced ICD discharge	26 (65%)
Experienced ICD discharge while driving	2 (7%)*
Asked insurance company and/or department of motor vehicles about driving with an ICD	4 (10%)

*These drivers denied dizziness, syncope, or loss of consciousness and continued to drive after the discharge.

Trappe H, Wenzlaff P, Grellman G. Should patients with implantable cardioverter-defibrillators be allowed to drive? Observations in 291 patients from a single center over an 11-year period. Journal of Interventional Cardiac Electrophysiology 1998; 2:193-201														
Key Questions Addressed	**1**		**2**		**3**		**4**		**5**					
							✓							
Research Question	Correlations between frequency of ICD device therapy during driving, occurrence of syncopal symptoms, and incidence of traffic crashes													
Study Design	Survey													
Population	**Inclusion Criteria**	Patients implanted with an ICD at a single center												
	Exclusion Criteria	Patients who had never driven												
	Study population characteristics	Patients were divided into two groups; drivers and non-drivers. Additional baseline characteristics in Table G-115.												
	Generalizability to CMV drivers	Unclear												
Procedures	All patients advised not to drive at all after ICD implantation. Patients were followed in the outpatient clinic every two months. The patient's pre- and post- implant driving behavior was evaluated by administering an oral systematic questionnaire. The questionnaire was re-administered 6 months later by a different interviewer. At follow-up visits, each patient was asked whether they had sensed a device discharge or experienced symptoms such as palpitations, syncope, or dizziness. The ICDs were interrogated, and all arrhythmia episodes were verified by interviews with relatives, treating physicians or both. When available, stored electrograms were retrieved and analyzed. Reports of any symptoms or discharges while driving, motor vehicle crashes, and resulting injuries were corroborated by interviews with the patients, physicians, and relatives. Circumstances of all crashes were verified by interviews with patients and relatives by two experienced cardiologists.													
Statistical Methods	Data for continuous variables are summarized and reported as mean value ±standard deviation. Statistical analyses were evaluated by unpaired Student's t-test and Fisher's exact test. P values <0.05 were considered significant. A multivariate analysis using tree classification and regression analyses were performed to identify ICD patients at risk for shocks or crashes (related to arrhythmia) while driving. Multivariate analysis was performed to estimate risk of crash causing serious or fatal injury.													
Quality Assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Score = 4.75	**NR**	**NR**	**NR**	**NR**	**Y**	**NR**	**NR**	**Y**	**Y**	**NR**			
	Category= Low	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
		26	**27**	**28**										
Relevant Outcomes Assessed	Driving behavior pre- and post- implant and post implant crashes													

Trappe H, Wenzlaff P, Grellman G. Should patients with implantable cardioverter-defibrillators be allowed to drive? Observations in 291 patients from a single center over an 11-year period. Journal of Interventional Cardiac Electrophysiology 1998; 2:193-201	
Results	The majority of patients drove less frequently and more carefully after ICD implant. During a mean follow-up of 38±26 months (range <1 to 24 months) 11 of 171 driving patients (6%) were involved in 11 motor vehicle crashes; one crash was the patient's fault; remaining 10 crashes were due to a second party. Eleven patients had ICD therapy while driving. Of these eleven, seven patients had 3rd generation ICDs. Stored electrograms showed ventricular fibrillation was the underlying arrhythmia in three patients, whereas four patients had ventricular tachycardia. VF/VT was terminated by ICD in five patients and antitachycardia pacing was successful in the remaining two patients. There were no significant differences among drivers and non-drivers in the incidence of ICD therapy, interval post-implant to first therapy or frequency of pre-therapy syncopal symptoms (Table G-116).
Authors' Comments	Authors reported that they performed a multivariate analysis in an attempt to determine which patients were at increased risk of syncope during ICD discharges. However, they were not able to identify predictive risk factors in their patient population. Multivariate analysis was performed to identify patients at risk for ICD discharges and crashes during driving. The analysis included data about age, gender, underlying disease, left ventricular ejection fraction, spontaneous arrhythmias before ICD implant, induced arrhythmias during the electrophysiology study, defibrillation threshold, antiarrhythmic drugs, other drugs (digitalis, diuretics, Ace inhibitors, nitrates), type of implanted device (monophasic or biphasic waveform shocks), ICD with or without antitachycardia pacing modalities). Authors were not able to estimate risk of a driving crash related to an arrhythmia and could not identify patients at risk of a crash causing serious or fatal injury. Results depend on patient recall and reliable reporting of crashes.

Table G-115: Patient Characteristics

	Nondrivers	Drivers	Total
No. patients	120	171	291
Males (%)	94 (78%)	160 (94%)	254 (87%)
Age (years)	57 ± 15	57 ± 10	57 ± 12
(range)	10–78	22–73	10–78
Mean follow-up	37 ± 22	38 ± 24	38 ± 26
(months)	<1–105	<1–124	<1–124
Underlying disease			
CAD	84 (70%)	114 (67%)	198 (68%)
DCM	17 (14%)	33 (19%)	50 (17%)
R/LVD	3 (3%)	9 (5%)	12 (4%)
Other	16 (13%)	15 (9%)	31 (11%)
Vessel disease			
0-VD	32 (27%)	61 (36%)	93 (32%)
1-VD	30 (25%)	33 (19%)	63 (22%)
2-VD	29 (24%)	41 (24%)	70 (24%)
3-VD	29 (24%)	36 (21%)	65 (22%)
Ejection fraction			
Mean EF (%)	37 ± 14	37 ± 15	37 ± 15
(range)	15–77	12–85	12–85
EF < 40%	80 (67%)	114 (67%)	194 (67%)
EF ≥ 40%	40 (33%)	57 (33%)	97 (33%)
Arrhythmia history			
VF	49(41%)	55 (32%)	104 (36%)
SMVT	36 (30%)	66 (39%)	102 (35%)
SMVT + VF	35 (29%)	50 (29%)	85 (29%)
Heart failure			
NYHA I	13 (11%)	28 (17%)	41 (14%)
NYHA II	44 (37%)	82 (48%)	126 (43%)
NYHA III	63 (52%)	61 (23%)	124 (43%)
No. of failed AAD	3 ± 2	3 ± 2	3 ± 2
(range)	1–9	1–13	1–13

Abbreviations: AAD = antiarrhythmic drugs; CAD = coronary artery disease; DCM = dilated cardiomyopathy; R/LVD = right/left ventricular dysplasia; EF = left ventricular ejection fraction; No. = number; NYHA = New York Heart Association functional class of heart failure; SMVT = sustained monomorphic ventricular tachycardia; VD = vessel disease; VF = ventricular fibrillation.

Table G-116: Incidence and Characteristics of ICD Shocks

	Nondrivers	Drivers	Total
No. of patients	120	171	291
Incidence of ICD-D			
Patients with shocks	97 (81%)	127 (74%)	224 (77%)
Mean incidence	17 ± 26	16 ± 22	16 ± 24
(range)	0–129	0–128	0–129
Time to first shock (months)			
Mean interval	9 ± 10	9 ± 12	9 ± 11
(range)	1–52	1–68	1–68
0–6	51 (53%)	66 (52%)	117 (52%)
6–12	24 (25%)	26 (20%)	50 (22%)
13–24	15 (15%)	23 (18%)	38 (17%)
25–36	5 (5%)	6 (5%)	11 (5%)
≥37	2 (2%)	6 (5%)	8 (4%)
Symptoms			
Syncope during shocks	7 (7%)	8 (6%)	15 (7%)

Abbreviations: ICD = implantable cardioverter defibrillator, No. = number, pts = patients

Study Summary Tables (Key Question 5)

Adachi K, Ohnishi Y, Yokoyama M. Risk stratification for sudden cardiac death in dilated cardiomyopathy using microvolt-level T-wave alternans. Jpn Circ J 2001;65:76-80					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To evaluate T-wave alternans (TWA) as a new predictor for arrhythmogenesis and prospectively compare it with conventional parameters for risk stratifications of sudden cardiac death (SCD) in patients with dilated cardiomyopathy (DCM)				
Study Design	Cohort				
Population	**Inclusion Criteria**	Presence of dilated cardiomyopathy			
	Exclusion Criteria	Presence of atrial fibrillation or if a permanent pacemaker had previously been implanted.			
	Study population characteristics	Eighty-two consecutive patients with DCM who were referred to the Kobe University School of Medicine Hospital between February 1997 and April 2000 (Table G-117 and Table G-118).			
	Generalizability to CMV drivers	Unclear			
Methods	All patients underwent both noninvasive and invasive evaluation, including a physical examination, 12-lead ECG, chest radiography, M-mode and 2-dimensional Doppler echocardiography, 24-h Holter monitoring, exercise stress testing, diagnostic cardiac catheterization with coronary angiography and left ventriculography. All patients were taken off their antiarrhythmic treatment.				
Statistical Methods	Data were expressed as mean ± SD. A chi-square test was used to compare categorical variables. The unpaired Student's t test was used to compare continuous variables. The cumulative probability of events determined by Kaplan-Meier method, and differences in the distribution of events were evaluated with the log rank test. Significant factors detected by univariate analysis were reassessed by multivariate analysis. Multivariate analysis was performed by means of a Cox regression analysis. Statistical significance was considered at a value of $P < 0.05$.				
Relevant Outcomes Assessed	Sudden cardiac death				
Results	Kaplan-Meier survival analysis showed that TWA, left ventricular ejection fraction (LVEF) (≤35%), non sustained ventricular tachycardia, and QT dispersion (QTd) (>90 ms) were significant univariate risk stratifiers ($p < 0.005$, $p < 0.005$, $p < 0.005$, and $p < 0.005$ respectively) (Table G-119). Multivariate Cox regression analysis showed that TWA and LVEF were statistically significant independent risk stratifiers ($p < 0.05$ and $p < 0.01$, respectively) A combination of TWA and LVEF identified high risk DCM patients ($p < 0.001$) (Table G-120).				
Authors' Comments	TWA for the electrical substrate and the LVEF for the hemodynamic function are useful risk stratifiers for patients with DCM. The authors recommended that analysis of TWA and determination of LVEF are useful screening tests for determining the indication for implantable cardioverter defibrillator (ICD) therapy, and thus lessening the risk of SCD, in patients with DCM. The risk of stratification in the subgroup of patients with an LVEF >35% was not evaluated due to the small sample size of the study.				

Evidence of Potential Source of Bias?

Biases pertaining to Design				Biases pertaining to Data Collection			Biases in Analysis
Membership Bias	Non-Respondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
No	No	No	No	No	No	No	Yes

Table G-117: Patient Characteristics

Patients (n)	*82*
Age (years)	*53±15*
Gender	
Male	*67 (81%)*
Female	*15 (19%)*
NYHA	*1.6±0.8*
Medication for heart failure	
Digoxin	*21 (26%)*
Diuretics	*31 (38%)*
ACEI	*56 (68%)*
• -blocker	*40 (49%)*

NYHA, New York Heart Association Class; ACEI, angiotensin-converting-enzyme inhibitor.

Table G-118: Patient Characteristics and Results of Risk Stratification Tests

	Group A	*Group B*	*p value*
Patients (n)	*10*	*54*	
Age (years)	*55±12*	*48±14*	*NS*
Gender			
Male	*9 (90%)*	*43 (80%)*	
Female	*1 (10%)*	*11 (20%)*	
NYHA	*1.9±1.0*	*1.5±0.8*	*NS*
BP (mmHg)			
Systole	*126±12*	*122±19*	*NS*
Diastole	*75±13*	*74±10*	*NS*
CTR (%)	*54±6*	*51±6*	*NS*
Medication			
Digoxin	*4 (40%)*	*15 (28%)*	*NS*
Diuretics	*3 (30%)*	*18 (33%)*	*NS*
ACEI	*6 (60%)*	*32 (59%)*	*NS*
• -blocker	*5 (50%)*	*22 (41%)*	*NS*
TWA	*9 (90%)*	*21 (39%)*	*<0.005*
LVDd (mm)	*66±6*	*60±10*	*NS*
LVEF (%)	*34±13*	*47±13*	*<0.01*
NSVT	*8 (80%)*	*18 (33%)*	*<0.01*
SAECG	*4 (40%)*	*11 (20%)*	*NS*
QTd (ms)	*76±33*	*67±18*	*NS*

Group A, arrhythmic events group; Group B, nonevent group; NYHA, New York Heart Association Class; BP, blood pressure; CTR, cardiothoracic ratio; TWA, T-wave alternans; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion.

Table G-119: TWA and Conventional Risk Markers as Predictors for Event-Free Survival

	Se (%)	Sp (%)	PPV (%)	NPV (%)	RR	p value (* ^{2} test)
TWA	90	61	30	97	10.2	0.0029
LVDd	30	85	27	87	2.06	0.2423
LVEF	70	80	39	93	5.96	0.0013
NSVT	80	67	31	95	5.85	0.0053
SAECG	40	80	27	88	2.18	0.1783
QTd	40	91	44	89	4.07	0.0102

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; TWA, T-wave alternans; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion.

Table G-120: Prediction of Event-Free Survival with Two Variable Model

	Se (%)	Sp (%)	PPV (%)	NPV (%)	RR	p value (* ^{2} test)
LVEF≤35% NSVT(+)	50	85	38	90	3.92	0.0111
LVEF≤35% SAECG(+)	20	94	40	86	2.95	0.1180
LVEF≤35% QTd >90ms	20	96	50	87	3.75	0.0405
LVEF≤35% TWA(+)	60	85	43	92	5.36	0.0015

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion; TWA, T-wave alternans.

Balanescu S, Dan Corlan A, Dorobantu M, Gherasim L. Prognosis value of heart rate variability after acute myocardial infarction. Med Sci Monit 2004;10(7): CR307-315					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To assess the 1-year prognosis value of heart rate variability (HRV) parameters for sudden death and total mortality in patients with acute myocardial infarction (AMI)				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with AMI admitted from January 1995-Decenber 2000 to the coronary units of two cardiology departments. Diabetics who may show diminished HRV because of autonomic neuropathy were allowed to participate to the study.			
	Exclusion Criteria	Patients with AMI in Killip IV class and cardiogenic shock; AMI and chronic renal failure because of the influence of this condition on the parameters of HRV; older than 75 at the time of AMI or those with any type of cancer; treated with class Ia. and class III anti-arrhythmic drugs between 10 and 20 days after AMI; chronic or persistent atrial fibrillation between 10 and 20 days after AMI			
	Study population characteristics	Variable / Value N 463 Age (years) mean± SD 60.3 ± 13.6 years Gender M/F 312/151 Beta blockers were prescribed more frequently in the reperfusion group (43.1% vs. 19.5%; p <0.001), which may be a potential explanation for better HRV indices in these patients. See Table G-121 for complete details.			
	Generalizability to CMV drivers	Unclear			
Methods	The investigators included 463 consecutive patients with AMI. 211 (45.8%) received pharmacological or mechanical reperfusion, the other 252 (54.2%) patients receiving conventional therapy (aspirin, anticoagulants, IV nitroglycerin, beta blockers, and ACE inhibitors) because of late presentation (>12h) or absolute or relative contraindications to thrombolysis. Time-domain (standard deviation of NN interval [SDNN], square root of the mean squared differences of successive NN interval [srMSSD]) and frequency-domain (low frequency [LF], high frequency [HF], total power) HRV parameters were calculated from 24-hour Holter ECG recordings 10-20 days after AMI.				
Statistical Methods	Data were analyzed with the Stat View 4.53 statistical package. Comparisons between groups were made with the Student *t*-test for continuous measures and with the chi-square or fisher exact tests for categorical variables. Regression analysis was used in particular cases to assess correlation between some continuous variables. All risk factors that resulted in significance based on the univariate analysis were entered in survival analysis using the Cox proportional hazard regression model to assess independent predictors of survival at 1 year after MI. Relative risks of survival were calculated for each significant parameter. Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank (Cox-Mantel) test for independent variables that determined mortality.				
Relevant Outcomes Assessed	One-year total mortality, sudden cardiac death				
Results	Total mortality at 1-year follow-up was 14.7 %(68 patients), while sudden death was observed in 22 patients (4.8%). Both were higher in patients treated conventionally. Higher mortality rates in patients				

Balanescu S, Dan Corlan A, Dorobantu M, Gherasim L. Prognosis value of heart rate variability after acute myocardial infarction. Med Sci Monit 2004;10(7): CR307-315	
	included in the conservative treatment group were correlated with lower ejection fraction (37.1 ± 8.3% vs. 43.8 ± 7.9%; p <0.0001) and higher prevalence of ventricular arrhythmias (VT/VF: 17.5% vs. 10.4%; p = 0.033) (Table G-122). Patients treated by reperfusion had higher HRV parameters reflecting both vagal and sympathetic activity (SDNN, total spectral power) as well as those experiencing only vagal output (rMSSD, HF power) than conventionally treated subjects (Table G-123). The variables independently correlating with 1-year survival were SDNN <50 msec, rMSSD <20 msec, LF/HF >2, non-sustained ventricular tachycardia, and left ventricular ejection fraction <40%. The prognosis values of HRV parameters for global mortality and sudden death are shown in Table G- 124.
Authors' Comments	HRV parameters have prognosis value independent from left ventricular ejection fraction and spontaneous ventricular arrhythmias one year after AMI. Reduction of mortality risk by reperfusion therapy does not decrease the prognosis utility of HRV after AMI. In this study the 1-year total mortality rate was 14.7%, and sudden death occurred in 4.8% of patients, which represents a high percentage for the thrombolytic era: contemporary studies found a general mortality rate of 5-6% and a 2% rate of sudden death 1-year after MI.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				Biases pertaining to Data Collection			Biases in Analysis
Membership Bias	Non-Respondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
No	No	No	No	No	No	No	Yes

Table G-121: Patient Characteristics

Characteristics		Reperfusion therapy (n=211)	Conservative treatment (n=252)	p
Age (mean ±SD)		60.3±13.6	60.9±12.6	0.63
Male sex (n;%)		150 (71.1)	162 (64.3)	0.13
Hypertension (n;%)		49 (23.2)	64 (25.4)	0.66
Smoking (n;%)		129 (61.1)	164 (65)	0.38
Diabetes (n;%)		55 (26)	69 (27.3)	0.83
Hypercholesterolemia (n;%)		134 (63.5)	162 (64.3)	0.92
AMI location	Anterior	122 (57.8)	154 (61.1)	0.5
	Postero-inferior	89 (42.2)	98 (38.9)	0.5
LV dysfunction at admission (n;%)		52 (24.6)	60 (23.8)	0.85
Acute pulmonary edema (n;%)		22 (10.4)	28 (11.1)	0.81
Killip class I + II (n;%)		184 (87.2)	222 (88.1)	0.77
Killip class III (n;%)		27 (12.8)	30 (11.9)	0.77
Maximum CK (UI, mean ±SD)		1401±547	1600±550	0.001
Maximum CK-MB (UI, mean ±SD)		165±61	207±56	<0.0001
Betablockers (n;%)		91 (43.1)	49 (19.5)	<0.001
ACE-I (n;%)		131 (62.1)	160 (63.5)	0.77

Table G-122: Clinical Events and LVEF-1 year after MI

Characteristics	Reperfusion therapy (n=211)	Conservative treatment (n=252)	p
Post MI angina (n;%)	56 (26.5)	134 (53.2)	<0.0001
Recurrent MI (n;%)	12 (5.7)	23 (9.1)	0.21
LV failure (n;%)	49 (23.2)	93 (36.9)	0.002
LV EF (mean ± SD)	43.8±7.9	37.1±8.3	<0.0001
VT/VF (n;%)	22 (10.4)	44 (17.5)	0.033
CABG (n;%)	18 (8.5)	41 (16.3)	0.016
Total mortality (n;%)	19 (9)	49 (19.4)	0.0015
Sudden death (n;%)	5 (2.4)	17 (6.7)	0.029

Table G-123: Independent Predictors of Total Mortality

	DF	Coef	Std. error	Coef/SE	Chi-square	P-to-remove	Exp (Coef)
SDNN <50:T	1	0.763	0.276	2.762	7.630	0.0057	2.144
rMSSD <20:T	1	2.067	0.406	5.098	25.994	<0.0001	7.905
LF/HF >2:T	1	1.380	0.363	3.803	14.463	0.0001	3.974
NSVT mom 21:T	1	0.65	0.259	2.507	6.284	0.0122	1.915
LVEF <40:T	1	0.982	0.489	2.011	4.042	0.0444	2.671

Model coefficients for: 365 days FU; Censor variable: 1 year death; Model: Cox proportional hazards; Step: 5

Table G- 124: Prognostic Value of Calculated HRV parameters for Global Mortality and Sudden Cardiac Death

Parameter	Sensitivity (%)		Specificity (%)		Positive predictive value (%)		Negative predictive value (%)	
	Total mortality	Sudden death	Total mortality	Sudden death	Total mortality	Sudden death	Total mortality	Sudden death
SDNN <50 msec	58	63	98	87	85	21	93	97
rMSSD <20 msec	82	45	73	75	35	8	96	96
Total spectral power <2500 msec^2	51	54	95	81	64	14	91	96
HF <700 msec^2	66	59	94	73	69	10	94	97
LF >1500 msec^2	27	14	96	93	59	10	88	95
LF/HF ratio >2	80	81	83	74	45	14	96	98

Buxton A, Lee K, Hafley G, Wyse G, Fisher J, Lehman M, Pires L, Gold M, Packer D, Josephson M, Prystowsky E, Talajic M. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: An analysis of patients enrolled in the multicenter unsustained tachycardia trial. Circulation. 2006;106:2466-2472					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To evaluate the relation between ejection fraction, inducible ventricular tachyarrhythmia, and modes of death for patients enrolled in the Multicenter Un-sustained Tachycardia Trial (MUSTT); to provide further information regarding how best to stratify sudden death risk in patients with chronic coronary heart disease and moderate reductions of ejection fraction (30% to 40%) compared with those with severely reduced left ventricular function (ejection fraction <30%)				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with coronary artery disease who did not receive antiarrhythmic therapy			
	Exclusion Criteria	None reported			
	Study population characteristics	A total of 2202 patients were enrolled in the study. Antiarrhythmic therapy was not used in 1,791 of the 2,202 patients. Four hundred and twenty-nine patients with inducible sustained ventricular tachyarrhythmia and 1,362 patients without inducible randomizable tachyarrhythmias received no antiarrhythmic therapy. The breakdown of these patients based on inducibility and ejection fraction is outlined in Table G-125.			
	Generalizability to CMV drivers	Unclear			
Methods	Patients were enrolled at 85 sites in the U.S and Canada after undergoing evaluation and appropriate treatment of myocardial infarction. Standardized protocol programmed stimulation was performed in the absence of antiarrhythmic drugs. Patients with sustained monomorphic ventricular tachycardia were randomly assigned to receive either antiarrhythmic therapy guided by serial electrophysiologic studies or no antiarrhythmic therapy. Patients in whom no randomizable tachyarrhythmia was induced at the baseline electrophysiological study were followed up without antiarrhythmic therapy in a registry.				
Statistical Methods	The distributions of baseline characteristics were summarized with medians and 25th and 75th percentiles for continuous variables and percentages for categorical variables. Group differences in baseline characteristics, baseline medication use, and ECG characteristics were assessed with the Wilcoxon rank-sum test and the X^2 test. All tests of significance were 2-tailed. Cumulative event rates and survival curves were calculated by the Kaplan-Meier method, and outcome differences were assessed with the Cox proportional hazards model.				
Relevant Outcomes Assessed	Cardiac death				
Results	The relation between ejection fraction and event rates was highly significant whether ejection fraction was treated as continuous or dichotomized variable (Table G-126). The 5-year mortality rate of all patients with ejection fraction <30% (54%) was significantly higher than that of patients having an ejection fraction ≥30% (36%, p = 0.001). The higher percentage of events that were arrhythmic among patients with inducible tachyarrhythmia appeared more distinct among patients with an ejection fraction ≥30% (61% of events were arrhythmic among inducible patients with ejection fraction ≥30% and only 42% among noninducible patients, p = 0.002).				

Buxton A, Lee K, Hafley G, Wyse G, Fisher J, Lehman M, Pires L, Gold M, Packer D, Josephson M, Prystowsky E, Talajic M. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: An analysis of patients enrolled in the multicenter unsustained tachycardia trial. Circulation. 2006;106:2466-2472	
Authors' Comments	Both low ejection fraction and inducible tachyarrhythmias identify patients with coronary disease at increased mortality risk. Ejection fraction does not discriminate between modes of death, whereas inducible tachyarrhythmia identifies patients for whom death, if it occurs, is significantly more likely to be arrhythmic, especially if ejection fraction is ≥30%.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				**Biases pertaining to Data Collection**			**Biases in Analysis**
Membership Bias	**Non-Respondent Bias**	**Volunteer Bias**	**Survivor Bias**	**Recall Bias**	**Withdrawal Bias**	**Measurement Bias**	**Confounding Factors**
No	No	Yes	No	No	No	No	Yes

Table G-125: Relation between Inducible Tachyarrhythmia, Ejection Fraction, and Kaplan Meier Event Rates among Untreated Patients in MUSTT

	Inducible			Noninducible		
	EF <30% (n=217)	EF ≥30% (n=212)	*P*	EF <30% (n=690)	EF ≥30% (n=672)	*P*
2-Year mortality	0.33	0.22	0.0046	0.26	0.15	0.0001
5-Year mortality	0.57	0.43		0.54	0.34	
2-Year AD/CA	0.21	0.16	0.0845	0.15	0.08	0.0001
5-Year AD/CA	0.40	0.30		0.31	0.17	

Inducible/noninducible indicates presence/absence of inducible sustained randomizable ventricular tachyarrhythmia at baseline electrophysiological study; EF, ejection fraction; mortality, total mortality rates; and AD/CA, rate of arrhythmic death and cardiac arrest.

P values refer to Cox model comparison of overall mortality and of AD/CA in patients with EF <30% vs ≥30%, respectively.

Table G-126: Adjusted Cox Models*

	Total Mortality			Arrhythmic Death or Cardiac Arrest		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
EF (5% decrease from EF 40% to 20%)	1.18	1.12, 1.25	0.0001	1.19	1.10, 1.29	0.0001
EF <30%	1.53	1.31, 1.78	0.0001	1.53	1.23, 1.89	0.0001
Inducibility	1.22	1.03, 1.44	0.0202	1.63	1.31, 2.02	0.0001

EF indicates ejection fraction.

*Adjusted for age, sex, race, duration (in beats) of longest episode of nonsustained ventricular tachycardia, number of vessels with 75% or greater stenosis, left bundle-branch block, intraventricular conduction delay, use of digitalis at baseline, previous myocardial infarction, prior bypass surgery, prior angioplasty, and symptoms of angina within 6 weeks before enrollment.

Hazard ratios for each end point are depicted, with ejection fraction treated as a continuous variable (EF, 5% decrease from EF 40% to 20%) and dichotomized around the median value (<30%).

La Rovere M, Pinna G, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi P, Traversi E, Cobelli F. **Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003; 107: 565-570**					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To assess the prognosis value of short-term heart rate variability (HRV) parameters for sudden, presumably arrhythmic death in a large population of patients with moderate to severe chronic heart failure (CHF)				
Study Design	Cohort				
Population	**Inclusion Criteria**	Derivation sample: 202 consecutive patients in sinus rhythm with moderate to severe chronic heart failure (CHF) referred between 1991 and 1995 for evaluation and therapy, including heart transplantation			
	Exclusion Criteria	Patients with pulmonary or neurological disease, recent myocardial infarction, or cardiac surgery (within the previous 6 months); recently changed therapy (last 2 weeks); or any other disease that limits survival; with atrial fibrillation or pacemaker implantation; clinically unstable			
	Study population characteristics	Derivation Sample Variable — Value N — 202 Age (years) median interquartile range — 54±13 yrs Gender percent M/F — 87%/13% Validation Sample N — 242 Age (years) median interquartile range — 54±12 yrs Gender percent M/F — 83%/17% Additional baseline characteristics are shown in Table G-127.			
	Generalizability to CMV drivers	Unclear			
Methods	A multivariate survival model for identification of sudden (presumably arrhythmic) death was developed with data from 202 consecutive patients with moderate to severe HRF referred between 1991 and 1995 (the derivation sample). Time and frequency-domain HRV parameters obtained from an 8' recording of ECG at baseline and during controlled breathing (12 - 15 breaths/min) were challenged against clinical and functional parameters. This model was then validated in 242 consecutive patients referred between 1996 and 2001 (validation sample).				
Statistical Methods	Significant univariate predictors in the same compartment of variables were analyzed jointly in a multivariate Cox model to identify the subset containing independent prognosis information. All selected variables were then use candidates for the final survival model. Kaplan-Meier survival curves were compared with the log-rank test. Because of the skewness in the distribution of some variables, descriptive statistics are given as median (interquartile range). Comparisons between groups were performed by the Mann-Whitney U test or chi-square test. A probability value <0.05 was considered				

La Rovere M, Pinna G, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi P, Traversi E, Cobelli F. **Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003; 107: 565-570**	
	significant.
Relevant Outcomes Assessed	Three-year total mortality, sudden cardiac death
Results	After 3 years' follow-up, total mortality was 37 % in the derivation sample and 22% in the validation sample. Sudden death occurred in 19 patients (9.4%) in the derivation sample and 20 (8%) in the validation sample. Results for univariate and multivariate predictors of sudden death include a significant association between LVEF ≤ 21% and arrhythmic mortality with relative risk [RR] of 2.6 (95% CI 1.1- to 6.5) (Table G-128). Sudden death was independently predicted by a model that included low-frequency power (LFP) of HRV during controlled breathing ≤13 ms[2] and left ventricular end-diastolic diameter ≥77mm (RR 3.7, 95% CI 1.5 to 9.3, and RR 2.6, 95% CI 1.0 to 6.3, respectively) (Table G-129). Results for univariate and multivariate predictors of sudden death in the Validation Sample are shown in Table G-130. The derivation model was also a significant predictor in the validation sample (P = 0.04). In the validation sample, LFP ≤11ms[2] during controlled breathing and ≥ 83 ventricular premature contractions per hour on Holter monitoring were both independent predictors of sudden death (RR 3.0, 95% CI 1.2 to7.6. and RR 3.7, 95% CI 1.5 to 9.0 , respectively).
Authors' Comments	Reduced short term LFP during controlled breathing is a powerful predictor of sudden death in patients with CHF that is independent of many other variables. These results refine the identification of patients who may benefit from prophylactic implantation of a cardiac defibrillator.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				**Biases pertaining to Data Collection**			**Biases in Analysis**
Membership Bias	**Non-Respondent Bias**	**Volunteer Bias**	**Survivor Bias**	**Recall Bias**	**Withdrawal Bias**	**Measurement Bias**	**Confounding Factors**
No	No	No	No	No	No	No	Yes

Table G-127: Baseline Clinical and Test Characteristics

Variables	Derivation Sample (n=202)	Validation Sample (n=242)	P
Clinical			
Age, y	54 (13)	54 (12)	0.64
Male, %	87	83	0.31
NYHA class II to III, %	88	88	0.32
Cause, %			
Ischemic	49	46	0.31
Idiopathic	45	45	
Valvular	4	4	
Other	2	5	
Echocardiographic			
LVEF, %	23 (8)	27 (11)	<0.0001
LVESD, mm	62 (14)	59 (16)	0.007
LVEDD, mm	72 (12)	69 (13)	0.02
Deceleration time, ms	115 (55)	135 (65)	0.011
Mitral regurgitation grade 3 to 4, %	36	34	0.22
Cardiopulmonary exercise testing			
Peak $\dot{V}O_2$, mL·kg^{-1}·min^{-1}	14 (6)	15 (6)	0.11
Holter			
VPCs/h, n	15 (48)	15 (63)	0.96
NSVT, %	38	39	0.85
QRS duration ≥120 ms, %	45	40	0.23
Blood chemistry			
BUN, mg/dL	49 (23)	46 (17)	0.01
Creatinine, mg/dL	1.19 (0.32)	1.05 (0.30)	<0.0001
Sodium, mEq/L	139 (5)	140 (4)	<0.0001
Potassium, mEq/L	4.3 (0.4)	4.4 (0.5)	0.11
Bilirubin, mg/dL	1.0 (0.48)	0.7 (0.5)	<0.0001
HRV			
Baseline RR interval, ms	823 (211)	834 (218)	0.05
Baseline SD, ms	21 (17)	21 (19)	0.94
Baseline LF power, ms^2	30 (101)	45 (96)	0.01
Baseline HF power, ms^2	32 (65)	40 (82)	0.06
LF/HF	1.08 (1.56)	1.41 (2.03)	0.02
Controlled-breathing R-R interval, ms	833 (206)	839 (271)	0.02
Controlled-breathing SD, ms	18 (15)	17 (14)	0.63
Controlled-breathing LF power, ms^2	28 (92)	41 (90)	0.04
Controlled-breathing HF power, ms^2	43 (108)	55 (112)	0.41
Therapy, %			
ACE inhibitors/AT_1 receptor antagonist	90	99	<0.001
Diuretics	96	85	<0.001
Nitrates	56	45	0.02
Digoxin	78	56	<0.001
β-Blockers	6	31	<0.001
Amiodarone	29	22	0.09

NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; VPCs/h, ventricular premature contractions/hour; NSVT, nonsustained ventricular tachycardia; and BUN, blood urea nitrogen.

Values are median (interquartile range [75th percentile−25th percentile]).

Table G-128: Significant Univariate Association of Risk Variables

Variables (Cutoff Value)	χ^2	*P*	RR (95% CI)
Echocardiographic			
LVEF (≤21%)	4.2	0.04	2.6 (1.1–6.5)
LVEDD (≥77 mm)	5.1	0.02	2.8 (1.1–6.9)
Holter monitoring			
VPCs (≥86/h)	3.7	0.05	2.3 (1.0–5.3)
Blood chemistry			
BUN (≥57 mg/dL)	4.7	0.03	2.6 (1.1–6.9)
Bilirubin (≥1.03 mg/dL)	4.2	0.05	2.7 (1.0–7.2)
HRV			
Baseline SD (≤21 ms)	7.3	0.007	4.6 (1.5–13.9)
Baseline LF power (≤11 ms^2)	5.9	0.01	3.1 (1.2–7.6)
Baseline LF/HF (≤0.37)	7.5	0.006	3.6 (1.4–9.0)
Controlled-breathing LF power (≤13 ms^2)	8.1	0.004	3.8 (1.5–9.4)

Abbreviations as in Table 1.

Table G-129: Multivariate Prognostic Model for Sudden Death in the Derivation Sample

Variables (Cutoff Value)	χ^2	*P*	RR (95% CI)
Controlled-breathing LF power (≤13 ms^2)	7.8	0.005	3.7 (1.5–9.3)
LVEDD (≥77 mm)	4.1	0.042	2.6 (1.0–6.3)

LVEDD indicates left ventricular end-diastolic diameter.

Table G-130: Multivariate Prognostic Model for Sudden Death in the Validation Sample

Variables (Cutoff Value)	χ^2	*P*	RR (95% CI)
VPCs/h (≥83)	7.9	0.005	3.7 (1.5–9.0)
Controlled-breathing LF power (≤11 ms^2)	5.7	0.017	3.0 (1.2–7.6)

VPCs indicates ventricular premature contractions.

Pedersen O, Abildstrom S, Ottesen M, Rask-Madsen C, Bagger H, Kober L, Torp-Pedersen C. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. European Heart Journal 2006; 27:290-295					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To examine the mode of death in patients with a recent myocardial infarction and Atrial Fibrillation (AF), to further clarify the cause of the excess mortality observed in several studies, and to examine whether there were likely to be subgroups with particularly high risk of sudden cardiovascular death (SCD) in relation to AF				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients > 18 years old, discharged after hospitalization for an acute myocardial infarction, screened in the TRAndolapril Cardiac Evaluation registry			
	Exclusion Criteria	Patients who died during hospitalization were removed from the analysis			
	Study population characteristics	See Table G-131 for complete details			
	Generalizability to CMV drivers	Unclear			
Methods	The study population consisted of 5983 patients with acute myocardial infarction admitted to 27 centers in Denmark from May 1990 to July 1992 and screened for inclusion into the TRAndolapril Cardiac Evaluation (TRACE) study. The criteria for myocardial infarction were chest pain and/or electrocardiographic changes suggestive of infarction or ischemia, accompanied by an increase of one or more cardiac enzymes to at least twice the upper limit of the normal value at the laboratory of the participating hospital. Clinical data including presence of AF/atrial flutter (AFL) were prospectively collected. Left ventricular systolic function was determined as wall motion index (WMI) by echocardiography. WMI multiplied by 0.3 provides an estimate of left ventricular ejection fraction (LVEF). In this study, the investigators reported estimated LVEF. Analysis of SCD and non-SCD included only events taking place after hospital discharge. An independent endpoint committee assessed the modes of death. Cardiovascular death was classified as SCD or non-SCD on the basis of the time elapsed from the onset of new symptoms to death. Only cardiovascular death with a period documented to be <1h was classified as SCD or in the case of patients found dead in bed without signs of preceding symptoms.				
Statistical Methods	Differences between groups with respect to medical history, clinical data, and complications during hospitalization were examined through the use of Chi square and Mann-Whitney tests for categorical and continuous variables, respectively. All tests were two-sided. P value<0.05 was considered significant. The unadjusted cause-specific mortality rates were compared with log-rank test. The association between AF/ALF and cause-specific mortality were examined through the use of a proportional hazard multivariate regression analysis (Cox regression analysis) while adjusting for appropriate baseline characteristics. LVEF was dichotomized at 40% and the risk ratio was estimated for patients with LVEF <40%, using LVEF >40% as the reference. All events rates were estimated for the maximal length of follow-up (4 years). All analyses were performed with the SAS system version 8.2.				
Relevant Outcomes Assessed	Survival status and mode of death in patients with AF and a recent myocardial infarction; risk of SCD and non-SCD				
Results	During the follow-up, 1659 patients (34%) died: 482 (50%) patients with AF/AFL and 1177 ((30%)				

Pedersen O, Abildstrom S, Ottesen M, Rask-Madsen C, Bagger H, Kober L, Torp-Pedersen C. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. European Heart Journal 2006; 27:290-295	
	without AF/AFL, P <0.001. SCD occurred in 536, non SCD occurred in 725, and 398 died of non-cardiovascular causes (includes 142 unclassified cases) (Table G-132). Results for LVEF are shown in Table G-133. Total mortality was increased by low LVEF RR: 1.57 (95% CI: 1.41 – 1.75; P <0.0001). Sudden cardiac death was increased by low LVEF RR: 1.73 (95% CI: 1.42- 2.09; P <0.0001). Non-sudden cardiac death was increased by low LVEF RR: 1.41 (95% CI: 1.19 – 1.65; P <0.0001). Risk of SCD associated with AF/ALF was increased in both patients with LVEF above and below 0.40. The investigators found a significant interaction between AF/ALF and LVEF for all-cause mortality (P <0.005), but not for sudden death (P = 0.45). It is of interest that SCD was increased in patients with LVEF above 40%, which is different from what would have been expected from recent trials of the implantable cardioverter defibrillator (ICD). This study raises the question whether some patients with LVEF above 40%, AF, and a recent myocardial infarction could benefit from ICD therapy.
Authors' Comments	The most important finding was that SCD and non-SCD were increased to a similar extent. The excess mortality observed in patients with AF/ALF following acute myocardial infarction is due to a significant increase in both SCD and non-SCD.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				Biases pertaining to Data Collection			Biases in Analysis
Membership Bias	Non-Respondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
No	No	No	No	No	Yes	No	Yes

Table G-131: Patient Characteristics

	Data availability (%)	AF/AFL ($n = 1149$)	No AF/AFL ($n = 4834$)	P-value
Age (years)	100	73	66	<0.001
Male gender	100	65%	70%	<0.002
History of hypertension	99.9	25%	22%	<0.02
History of diabetes	99.9	13%	10%	<0.002
History of angina pectoris	99.9	38%	36%	0.2
Previous myocardial infarction	99.7	23%	23%	0.8
In-hospital VF	100	7%	4%	<0.001
In-hospital VT	100	16%	10%	<0.001
QRS > 120 ms	99.5	11%	6%	<0.001
LVEF	95.7	0.39	0.45	<0.001
CHF	100	69%	45%	<0.001

Table G-132: Cause-Specific 4-year Mortality Probabilities

	AF/AFL ($n = 1149$) (%)	No AF/AFL ($n = 4834$) (%)	P-value
All deaths	482 (50)	1177 (30)	<0.001
Non-cardiovascular death	111 (12)	287 (8)	<0.001
Cardiovascular death	371 (38)	890 (22)	<0.001
Non SCD	222 (22)	503 (12)	<0.001
SCD	149 (16)	387 (10)	<0.001

Table G-133: Comparison of Different Independent Risk Factors for Total Death, Sudden-Death and Non-Sudden Death

	Total death RR (95% CI)	P-value	SCD RR (95% CI)	P-value	Non-SCD RR (95% CI)	P-value
Age	1.60 (1.51–1.70)	0.0001	1.28 (1.67–1.41)	0.0001	1.82 (1.67–1.99)	0.0001
Sex	1.14 (1.02–1.27)	0.02	1.30 (1.07–1.59)	0.0098	1.04 (0.88–1.23)	0.64
EF	1.57 (1.41–1.75)	0.0001	1.73 (1.42–2.09)	0.0001	1.41 (1.19–1.65)	0.0001
Pre-MI	1.18 (1.05–1.32)	0.007	1.25 (1.01–1.54)	0.035	1.14 (0.95–1.36)	0.15
CHF	1.97 (1.74–2.22)	0.0001	2.12 (1.71–2.63)	0.0001	1.95 (1.62–2.36)	0.0001
Angina	1.30 (1.30–1.45)	0.0001	1.22 (1.00–1.49)	0.043	1.69 (1.41–1.98)	0.0001
Diabetes	1.50 (1.31–1.72)	0.0001	1.43 (1.12–1.82)	0.0041	1.62 (1.33–1.98)	0.0001
Hypertension	1.22 (1.09–1.37)	0.0007	1.35 (1.11–1.64)	0.0027	1.29 (1.09–1.53)	0.003
BBB	1.51 (1.30–1.76)	0.0001	1.58 (1.22–2.06)	0.0005	1.47 (1.17–1.85)	0.0009
AF/AFL	1.33 (1.19–1.49)	0.0001	1.31 (1.07–1.60)	0.009	1.43 (1.21–1.70)	0.0001

EF, ejection fraction; Pre-MI, previous myocardial infarction; BBB, bundle branch block.

<table>
<tr><td colspan="7">Raczak G, Pinna G, Maestri R, Danilowicz-Szymanowicz L, Szwoch M, Lubinski A, Kempa M, La Rovere M, Swiatecka G. Different predictive values of electrophysiological testing and autonomic assessment in patients surviving a sustained arrhythmic episode. Circ J 2004 ;68: 634-638</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td></td><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>Research Question</td><td colspan="5">To evaluate the predictive value of electrophysiological testing together with non-invasive measurement of baroreflex sensitivity (BRS) in patients surviving a sustained arrhythmic episode</td></tr>
<tr><td>Study Design</td><td colspan="5">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="4">Post myocardial infarction patients consecutively referred for an electrophysiological study. (EPS) following documented ventricular fibrillation VF or documented sustained ventricular tachycardia (SVT) or a syncopal episode in the presence of non-sustained VT on 24-h Holter recording; patients clinically stable and free from angina</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="4">Patients with atrial fibrillation; sinus node dysfunction; atrioventricular block; insulin-dependent diabetes; frequent (>5%) ectopic beats</td></tr>
<tr><td>Study population characteristics</td><td colspan="4"><u>Variable</u> <u>Value</u>
n 112
Age (years) mean±SD 61±10 yrs
Gender M/F 90/22
LVEF % 37 ±12

Additional baseline characteristics are shown in Table G-134.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="4">Unclear</td></tr>
<tr><td>Methods</td><td colspan="5">All 112 patients underwent clinical evaluation, electrophysiological and echocardiographic studies and BRS assessment. A cardioverter-defibrillator (ICD) was implanted in 97 patients and the remaining 15 patients were treated with amiodarone or blocker. Patients were followed up for a median of 315 days.</td></tr>
<tr><td>Statistical Methods</td><td colspan="5">Continuous variables in the event + and event – groups were compared by t-test for independent samples or, in case of violation of the normality assumption, by the Mann-Whitney test. Categorical variables were compared by the chi-square test. A p-value <0.05 was considered significant. Survival analysis was performed after categorization of continuous variables. The univariate predictive value of each variable was assessed by the proportional hazards regression analysis. Results are presented as relative risk (RR) and corresponding 95% confidence interval (CI). Event –free curves were estimated by the Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed by the SAS-STAT statistical package.</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="5">Sudden cardiac death, arrhythmia recurrence</td></tr>
<tr><td>Results</td><td colspan="5">Sudden (presumably arrhythmic) death was defined as death occurring within 1 hour of onset of symptoms in a previously medically stable patient, death during sleep or unwitnessed death occurring within 1 hour of the patient being last seen alive. During follow-up, appropriate ICD discharge occurred in 53 patients, and 3 more patients died suddenly. Results for univariate predictors of arrhythmia recurrence include left ventricular ejection fraction (LVEF) ≤35%, New York</td></tr>
</table>

Raczak G, Pinna G, Maestri R, Danilowicz-Szymanowicz L, Szwoch M, Lubinski A, Kempa M, La Rovere M, Swiatecka G. Different predictive values of electrophysiological testing and autonomic assessment in patients surviving a sustained arrhythmic episode. Circ J 2004 ;68: 634-638	
	Heart Association (NYHA) class >2 and BRS ≤3.3 ms / mmHg (Table G-135). A depressed BRS (≤3.3 ms / mmHg) showed the strongest association with the occurrence of an event with RR of 2.3 (95%CI 1.3-4.0) followed by LVEF ≤ 35% with RR of 2.0 (95% CI 1.2 – 3.6). Multivariate prognostic model (Table G-136) was obtained after grouping the patients according to moderately or severely depressed LVEF. Among the patients with LVEF ≤35%, BRS ≤3.3 ms / mmHg emerged as the only significant risk predictor of arrhythmia occurrence (sensitivity, specificity, positive and negative predictive value = 79%, 83%, and 68% respectively) whereas NYHA class >2 was a significant predictor among patients with LVEF >35%.
Authors' Comments	Noninvasive BRS, but not EPS, is of value in predicting VT/VF episode recurrence in patients surviving a major arrhythmic event. Electrophysiological testing in patients who survived a sustained arrhythmic event following MI is poorly predictive of future sudden death, whereas autonomic markers together with indexes of left ventricular function can help to cost-effectively identify patients at increased risk of arrhythmia recurrence who do warrant ICD implantation.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				**Biases pertaining to Data Collection**			**Biases in Analysis**
Membership Bias	**Non-Respondent Bias**	**Volunteer Bias**	**Survivor Bias**	**Recall Bias**	**Withdrawal Bias**	**Measurement Bias**	**Confounding Factors**
No	No	No	No	No	No	No	Yes

Table G-134: Patient Characteristics

	Overall group	Event (+)	Event (–)	p value
n	112	56	56	
Age (years)	61±10	60±10	62±9	0.20
M/F	90/22	44/12	46/10	0.63
LVEF (%)	37±12	34±10	39±13	0.022
NYHA (%)				
I	21	16	27	
II	42	38	46	0.08
III	37	46	27	
No. of MI	1.2±0.4	1.2±0.5	1.2±0.4	0.78
Site of MI (%)				
Anterior	48	49	46	
Inferior	33	29	38	0.57
Other	19	22	16	
Inducible VT (%)	80	84	77	0.34
CL of induced VT (ms)	315±59	321±66	308±51	0.66
Antiarrhytmic drugs (%)				
• -blockers	28	27	29	
Amiodarone	38	43	34	0.59
None	34	30	37	
Resting RR (ms)	948±194	972±167	924±215	0.20
Resting SAP (mmHg)	102±18	102±14	101±21	0.91
BRS (ms/mmHg)	4.3±3.4	3.2±2.5	5.4±3.8	<0.001

VT, ventricular tachyacardia; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAP, systolic arterial pressure.

Table G-135: Significant Univariate Predictor of an Event

Variables (cut-off value)	• ²	p value	RR	95%CI
LVEF ≤35%	6.1	0.013	2.0	1.2–3.6
NYHA >2	4.4	0.036	1.8	1.1–3.0
BRS ≤3.3 ms/mmHg	8.4	0.004	2.3	1.3–4.0

RR, relative risk; CI, confidence interval (see Table 1 for other abbreviations).

Table G-136: Multivariate Prognostic Model

Variables (cut-off value)	• ²	*p value*	*RR*	*95%CI*
LVEF >35%				
NYHA >2	*5.4*	*0.02*	*3.1*	*1.2–8.0*
LVEF ≤35%				
BRS ≤3.3 ms/mmHg	*9.1*	*0.002*	*3.3*	*1.5–7.3*

Sharir T, Germano G, Kang X, Lwein H, Miranda R, Cohen I, Agafitei R, Friedman J, Berman D. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the post stress ejection fraction. J Nucl Med 2001;42:831-837					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					✓
Research Question	To determine the value of gated myocardial perfusion SPECT in the assessment of outcome-specific [nonfatal myocardial infarction (MI) vs. cardiac death (CD)] independent predictors; to examine the values of integrating perfusion and function data in stratifying patients into subsets with low, intermediate, and high risk CD				
Study Design	Cohort				
Population	**Inclusion Criteria**	Patients with ischemic cardiomyopathy and significant valvular pathology			
	Exclusion Criteria	Patients with nonischemic cardiomyopathy or significant valvular disease; have underwent revascularization within 60 days after the nuclear testing were censored from the prognostic portion of the analysis			
	Study population characteristics	Table G-137 summarizes clinical, scintigraphic, and follow-up data on the 2,686 patients who were included in the prognostic evaluation.			
	Generalizability to CMV drivers	Unclear			
Methods	The study identified 2,686 patients who underwent resting ^{201}Tl/stress ^{99m}Tc-sestamibi gated SPECT and were monitored for >1 year. Patients who underwent revascularization $\leq$60 days after the nuclear test were censored from prognostic analysis. Visual scoring of perfusion images used 20 segments and a scale of 0 – 4. Post-stress ejection fraction (EF) was automatically generated.				
Statistical Methods	Comparisons between patient groups were performed using 1-way ANOVA for continuous variables and the X^2 test for categorical variables. Cox proportional hazards regression analysis was applied to determine the independent predictors of CD and nonfatal MI as separate end points. Multivariate analysis was performed in a stepwise fashion and the pre scan likelihood of coronary artery disease (CAD) was calculated using the microcomputer program CADENZA, which is based on Bayesian analysis of pre scan patient data. Kaplan-Meier survival analysis with stratification by EF and summed difference score (SDS) was performed. Survival curves were compared by the log rank test. Correlations between the CD rate and EF and between the MI and the SDS were evaluated using ANOVA. The statistical analysis was performed using the Graduate Pack 9.0 (SPSS).				
Relevant Outcomes Assessed	CD, MI				
Results	Cox regression analysis showed that after adjusting for pre scan data, the most powerful predictor of CD was post-stress EF, whereas the best predictor of MI was the amount of ischemia (summed difference score [SDS]) (Table G-138). Integration of the EF and SDS yielded effective stratification of patients into low-, intermediate-, and high-risk subgroups. Patients with EF >50% and a large amount of ischemia were at intermediate risk (2%-3%), whereas those with mild or moderate ischemia were at low risk of CD (<1%/ year). Patients with EF between 30% and 50% were at intermediate risk even in the presence of only mild or moderate ischemia. In patients with EF <30%, the CD rate was high (>4%/year) irrespective of the amount of ischemia.				

Sharir T, Germano G, Kang X, Lwein H, Miranda R, Cohen I, Agafitei R, Friedman J, Berman D. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the post stress ejection fraction. J Nucl Med 2001;42:831-837	
Authors' Comments	Post-stress EF is the best predictor of CD, whereas the amount of ischemia is the best predictor of nonfatal MI. Integration of perfusion and function data improves stratification of patients into low, intermediate, and high risk of CD and can assist in determining the appropriate treatment strategy for the individual patient.

Evidence of Potential Source of Bias?							
Biases pertaining to Design				Biases pertaining to Data Collection			Biases in Analysis
Membership Bias	Non-Respondent Bias	Volunteer Bias	Survivor Bias	Recall Bias	Withdrawal Bias	Measurement Bias	Confounding Factors
No	No	No	No	No	Yes	No	Yes

Table G-137: Patient Characteristics

Parameter	*n* (%)
Patients	2,686
Age (y)	66 ± 12
Males	1,636 (60.9)
Exercise	1,678 (62)
Symptoms	
Typical angina	403 (15)
Atypical angina	798 (29.7)
History of MI	698 (26)
History of coronary angioplasty	518 (19.3)
History of bypass surgery	525 (19.5)
Diabetes mellitus	313 (12)
Hypertension	1,284 (47.8)
Current smoking	259 (9.6)
Prescan likelihood of CAD	0.38 ± 0.31
Abnormal perfusion at stress	1,440 (53.9)
Reversible perfusion defect	1,261 (47)
EF	58 ± 5
CD	57 (2.12)
MI	30 (1.12)

Table G-138: Multivariate Cox Proportional Hazards Analysis

Parameter	β coefficient	SE	Wald χ^2	*P*
MI				
SDS	0.09	0.02	17.03	<0.0001
Prescan likelihood of CAD	1.74	0.68	6.55	0.01
CD				
EF	−0.05	0.01	24.35	<0.0001
Adenosine stress	1.22	0.35	11.89	0.0006
Prescan likelihood of CAD	1.57	0.64	5.97	0.02

Solomon S, Zelenkofske S, McMurray J, Finn P, Velazquez E, Ertl G, Harsanyi A, Rouleau J, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf R, Pfeffer M. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both. NEJM 2005;23:2581-2588					
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**
					√
Research Question	To assess the risk and time course of sudden death in high-risk patients after myocardial infarction (MI)				
Study Design	Cohort				
Population	**Inclusion Criteria**	All patients with an ejection fraction of no more than 40% or clinical radiologic evidence of heart failure complicating their MI			
	Exclusion Criteria	Patients who had received an implantable cardioverter-defibrillator (ICD) before randomization			
	Study population characteristics	A total of 14,609 patients with left ventricular dysfunction, heart failure or both after MI (Table G-139).			
	Generalizability to CMV drivers	Unclear			
Methods	A central adjudication committee reviewed all death episodes of cardiac arrest with resuscitation in a blinded fashion, using documentation provided by the site investigators. The median follow-up was 24.7 months.				
Statistical Methods	The rates of sudden death were assessed by dividing the events in each period by the number of person-days of exposure and are expressed as the percentage per month. Baseline clinical characteristics were compared with the use of the Student's t-test for continuous variables and the chi-square test for categorical variables. The risk of sudden death associated with each decrease of 5 percentage points in the left ventricular ejection fraction was assessed in a Cox proportional-hazards model, with adjustment for all known baseline covariates.				
Relevant Outcomes Assessed	Sudden unexpected death, cardiac arrest				
Results	Of the 14,609 patients, 1067 (7%) had an event a median of 180 days after myocardial infarction. The risk was highest in the first 30 days after myocardial infarction-1.4% per month (95% CI, 0.11 – 1.6)-and decreased to 0.14% per month (95% CI, 0.11 – 0.18) after 2 years (Table G-140).				
Authors' Comments	The risk of sudden death is highest in the first 30 days after MI among patients with left ventricular dysfunction, heart failure, or both. Earlier implementation of strategies for preventing sudden death may be warranted in selected patients.				

Evidence of Potential Source of Bias?							
Biases pertaining to Design				**Biases pertaining to Data Collection**			**Biases in Analysis**
Membership Bias	**Non-Respondent Bias**	**Volunteer Bias**	**Survivor Bias**	**Recall Bias**	**Withdrawal Bias**	**Measurement Bias**	**Confounding Factors**
No	No	Yes	No	No	No	No	Yes

Table G-139: Baseline Characteristics

Characteristic	Sudden Death or Cardiac Arrest with Resuscitation (N=1067)	Death from Cause Other Than Sudden Death (N=1905)	P Value	Survival Free of Sudden Death or Cardiac Arrest with Resuscitation (N=11,637)	P Value†
Age (yr)	67.8±11.2	71.4±10.3	<0.001	63.5±11.7	<0.001
Male sex (%)	67	61	0.002	70	0.04
Blood pressure (mm Hg)					
Systolic	125.1±18.2	123.5±17.5	0.02	122.3±17.0	<0.001
Diastolic	73.3±12.0	71.9±11.9	0.002	72.3±11.1	0.008
Heart rate (beats/min)	78.1±13.6	78.9±13.7	0.10	75.6±12.5	<0.001
Body-mass index	27.7±5.7	27.1±5.0	0.007	28.0±5.3	0.04
Killip class (%)			0.13		<0.001
I	19	17		30	
II	46	47		49	
III	26	26		15	
IV	9	10		5	
Clinical or radiologic evidence of CHF at entry (%)	83	85	0.10	75	<0.001
Prior myocardial infarction (%)	45	41	0.08	24	<0.001
History of hypertension (%)	64	64	0.96	53	<0.001
History of diabetes (%)	31	32	0.42	21	<0.001
Beta-blocker (%)	61	57	0.07	73	<0.001
Amiodarone (%)	20	19	0.73	8	<0.001
Primary PCI (%)	8	8	0.34	17	<0.001
Thrombolytic therapy (%)	24	25	0.32	38	<0.001
Primary PCI or thrombolytic therapy (%)	30	32	0.25	49	<0.001
LVEF	0.32±0.10	0.33±0.10	0.06	0.36±0.10	<0.001

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Percentages may not sum to 100 because of rounding. CHF denotes congestive heart failure, PCI percutaneous coronary intervention, and LVEF left ventricular ejection fraction.
† P values are for the comparison with sudden death or cardiac arrest with resuscitation.

Table G-140: Event Rate and Cumulative Incidence of Events during Follow up

Time after Myocardial Infarction	No. at Risk at Beginning of Interval	No. Who Died of Any Cause during Interval	Sudden Death or Cardiac Arrest with Resuscitation		
			No. of Patients	Event Rate %/mo (95% CI)	Cumulative Incidence %
0–30 Days	14,609	589	198	1.4 (1.2–1.6)	1.4
>1–6 Mo	13,997	767	340	0.50 (0.45–0.55)	2.5
>6–12 Mo	13,157	509	211	0.27 (0.23–0.31)	1.6
>1–2 Yr	12,622	754	240	0.18 (0.16–0.20)	2.1
>2–3 Yr	7,926	244	75	0.14 (0.11–0.18)	1.7

* CI denotes confidence interval.

Appendix H: Sensitivity Analyses

Sensitivity Analyses (Key Question 1)

CVD (any) and RR

Figure H-1. Random -effects Meta-analysis

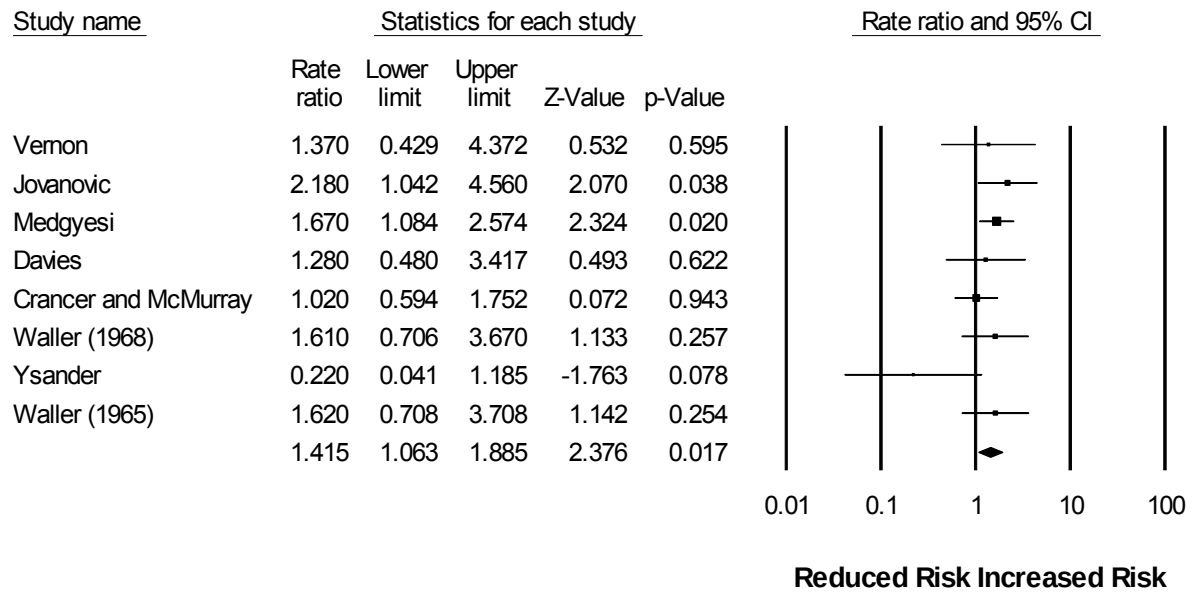
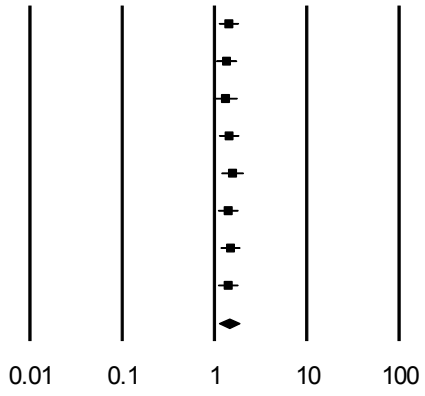


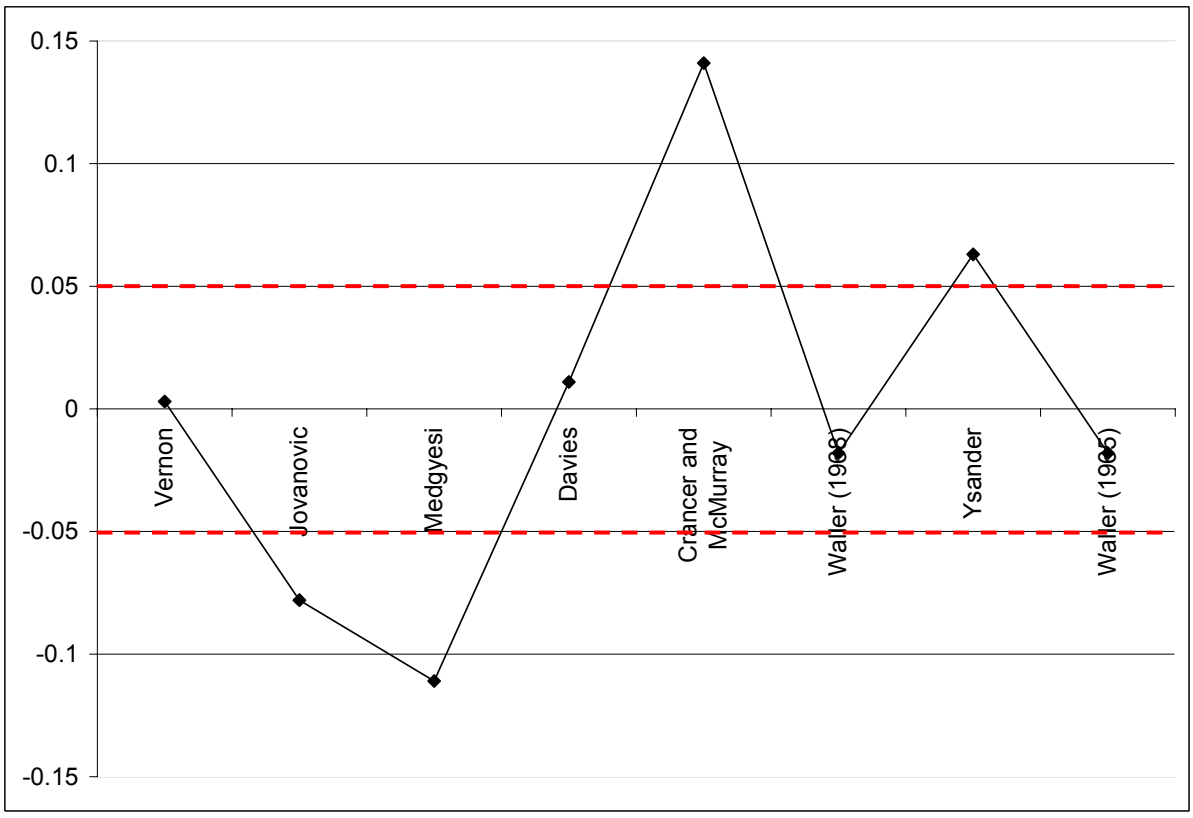
Table H-1. Findings of Random-effects and Fixed-effects Meta-analysis

Model	Summary RR	Lower 95% CI	Upper 95% CI	P =
Fixed-Effects	1.430	1.111	1.841	0.006
Random-Effects	1.415	1.063	1.885	0.017

Figure H-2. Removal of One Study at a Time

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.433	1.106	1.856	2.723	0.006
Jovanovic	1.352	1.033	1.769	2.198	0.028
Medgyesi	1.319	0.966	1.801	1.745	0.081
Davies	1.441	1.110	1.872	2.739	0.006
Crancer and McMurray	1.571	1.181	2.091	3.099	0.002
Waller (1968)	1.412	1.083	1.842	2.549	0.011
Ysander	1.493	1.156	1.928	3.073	0.002
Waller (1965)	1.412	1.083	1.841	2.546	0.011
	1.430	1.111	1.841	2.773	0.006

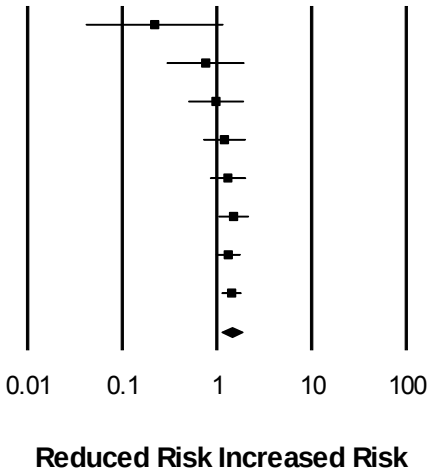


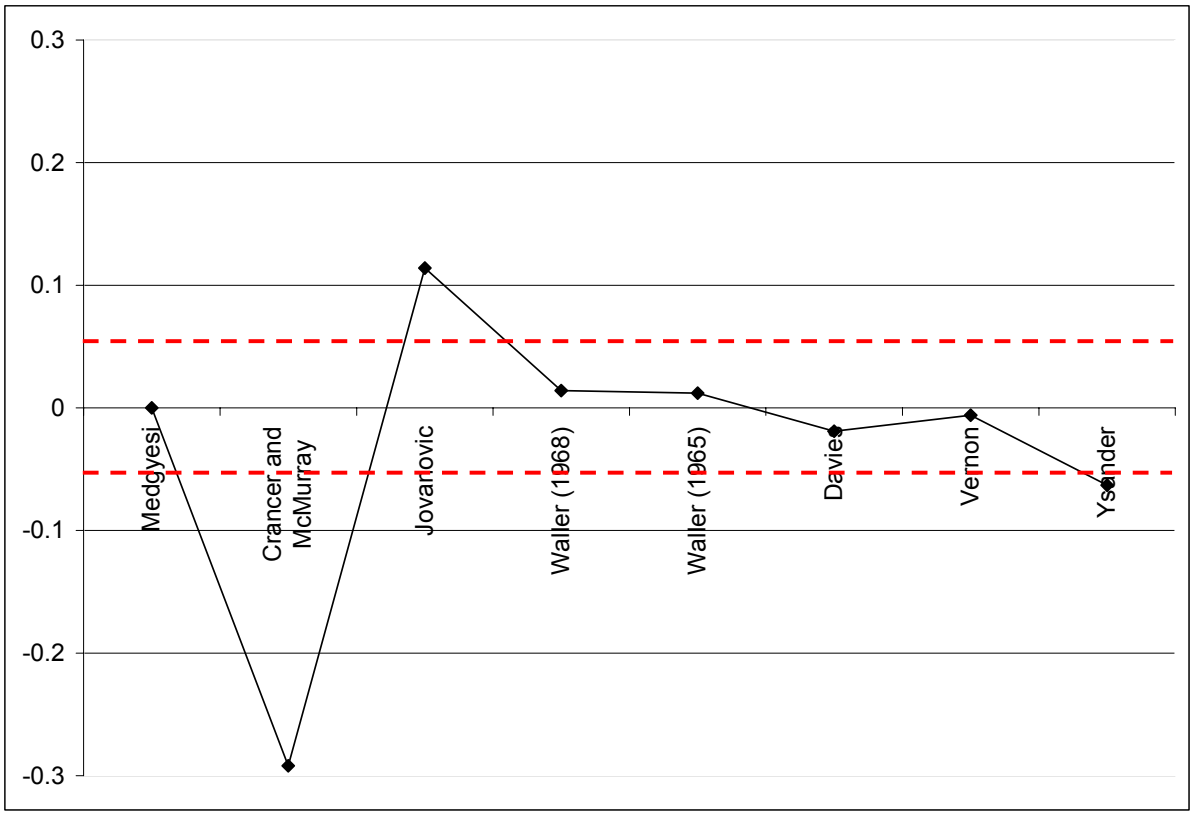


Removal of 1 study at a time resulted in changes in summary RR of greater than 5% from findings of primary analysis (four cases). The findings of our original analysis are not robust.

Figure H-3. Cumulative FEMA (Highest Weight Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Ysander	0.220	0.041	1.185	-1.763	0.078
Vernon	0.760	0.292	1.976	-0.563	0.574
Davies	0.979	0.494	1.943	-0.059	0.953
Waller (1965)	1.201	0.709	2.037	0.682	0.495
Waller (1968)	1.308	0.839	2.040	1.185	0.236
Jovanovic	1.499	1.024	2.193	2.083	0.037
Crancer and McMurray	1.319	0.966	1.801	1.745	0.081
Medgyesi	1.430	1.111	1.841	2.773	0.006
	1.430	1.111	1.841	2.773	0.006

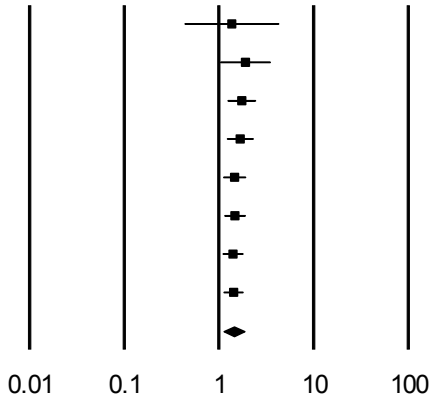


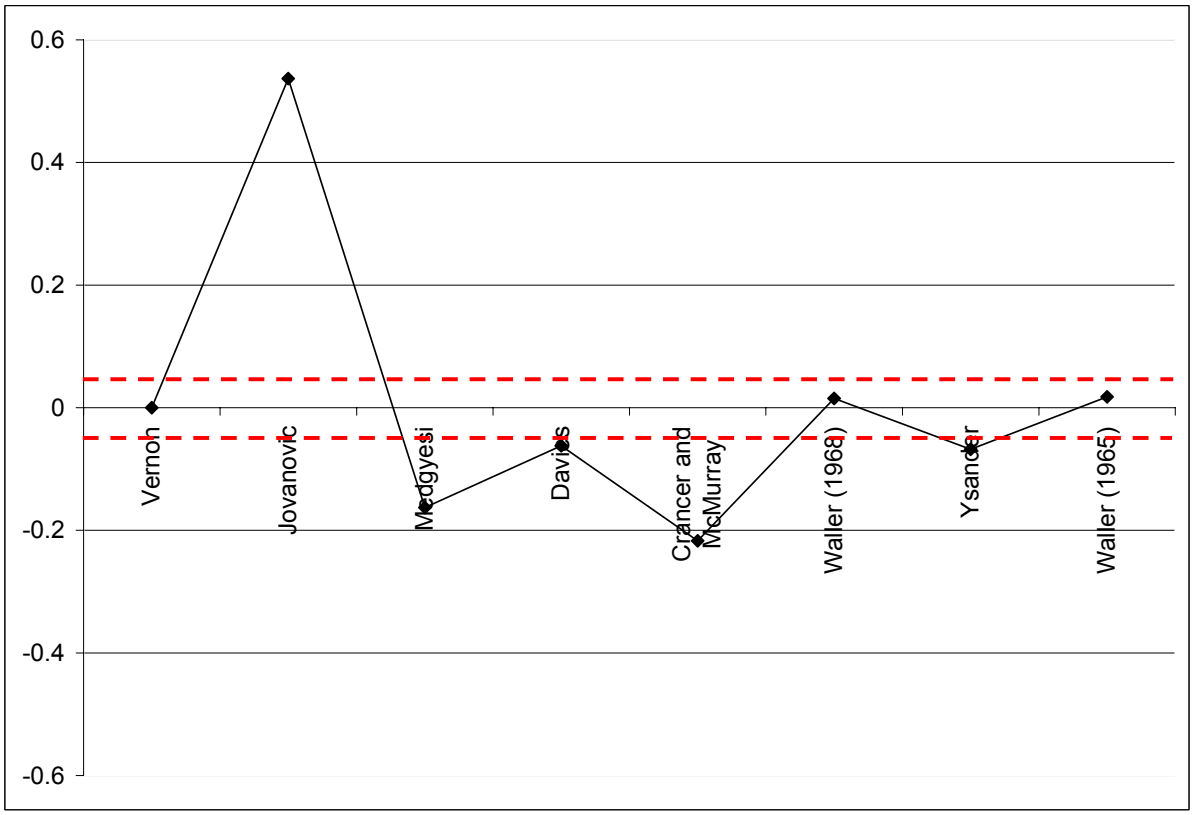


Change associated with addition of last three studies exceeds 5% tolerance limits. Findings of our original meta-analysis are not robust.

Figure H-4. Cumulative FEMA (Most Recent Study First)

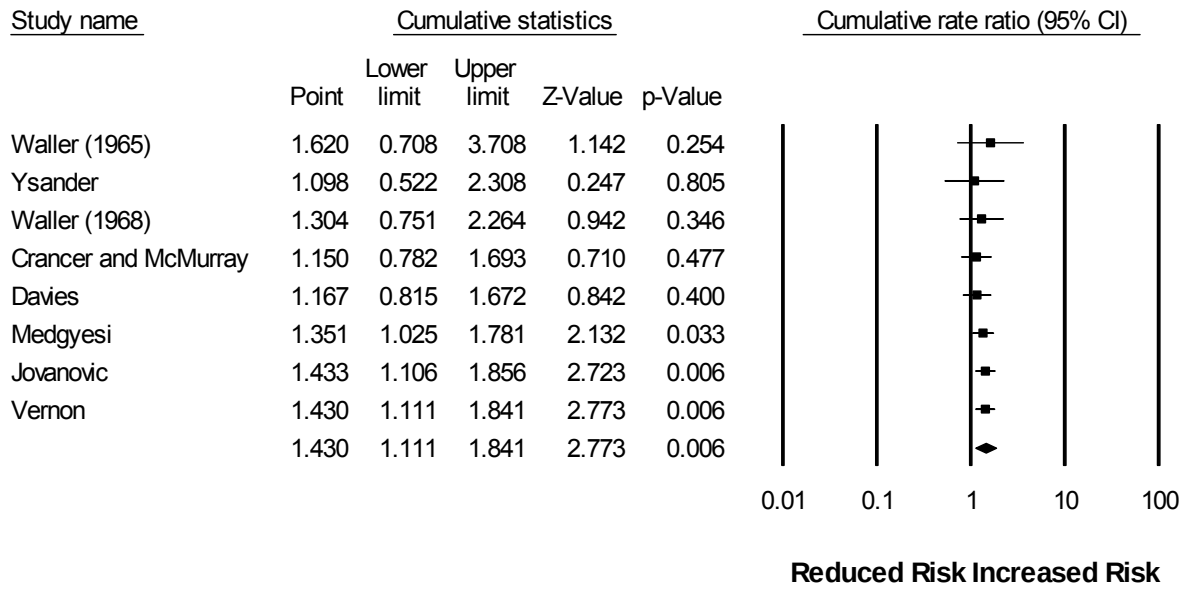
Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.370	0.429	4.372	0.532	0.595
Jovanovic	1.907	1.023	3.555	2.032	0.042
Medgyesi	1.744	1.222	2.488	3.068	0.002
Davies	1.682	1.205	2.350	3.052	0.002
Crancer and McMurray	1.465	1.103	1.947	2.635	0.008
Waller (1968)	1.480	1.131	1.936	2.860	0.004
Ysander	1.412	1.083	1.841	2.546	0.011
Waller (1965)	1.430	1.111	1.841	2.773	0.006
	1.430	1.111	1.841	2.773	0.006





Change associated with the addition of the last three studies exceeds 5% tolerance limits. Findings of our original meta-analysis are not robust.

Figure H-5. Cumulative FEMA (Oldest Study First)



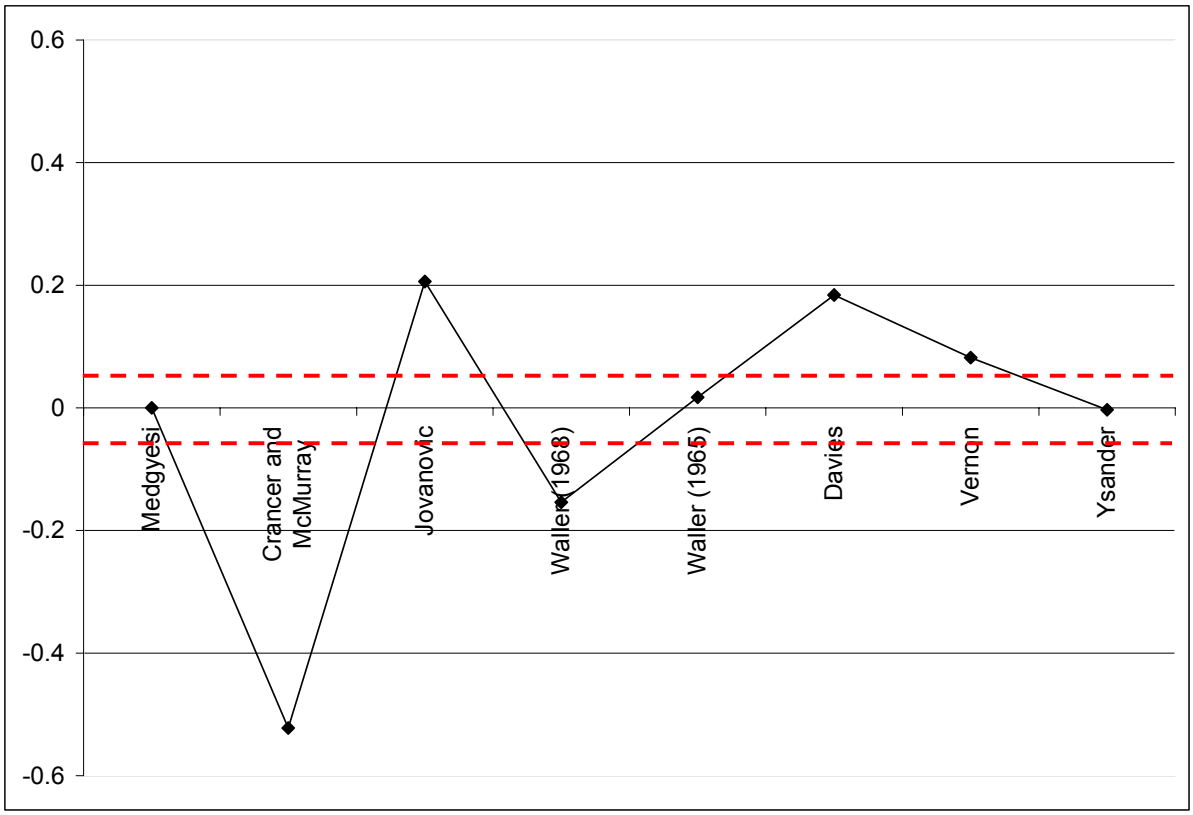
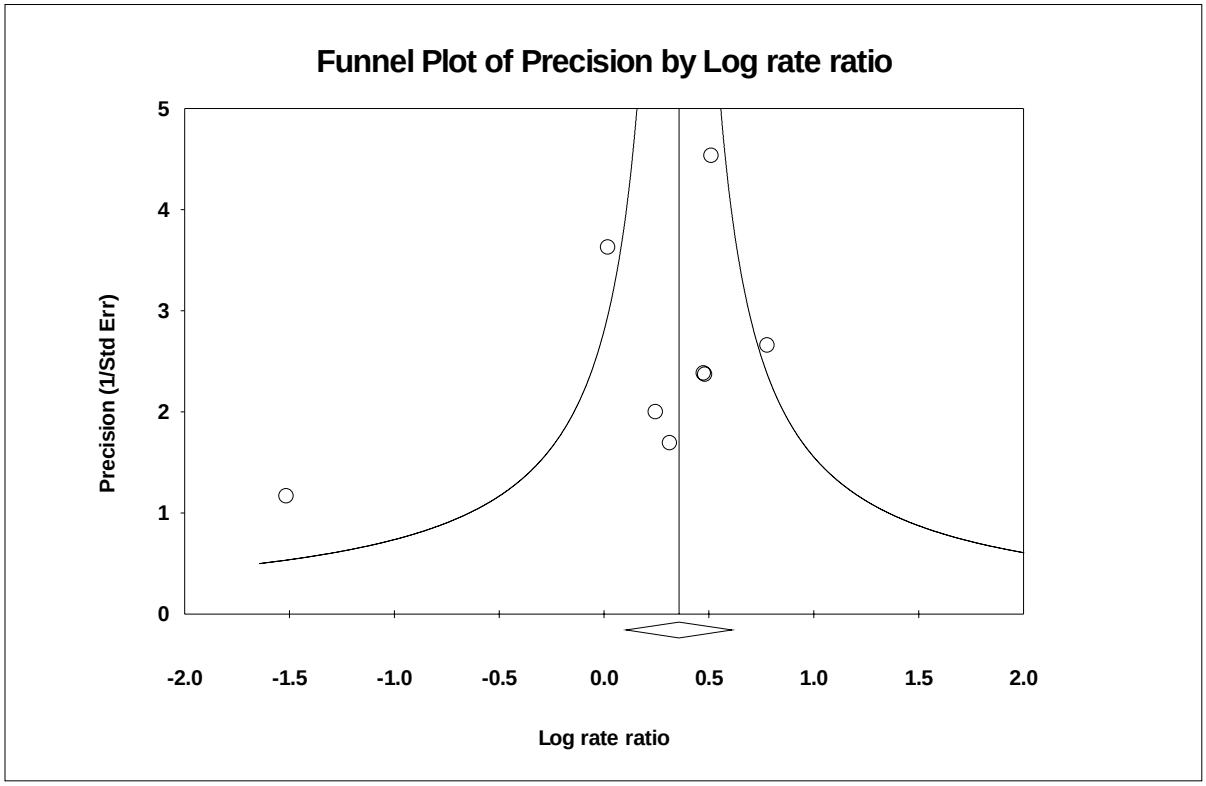

0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Medgyesi
Crancer and McMurray
Jovanovic
Waller (1968)
Waller (1965)
Davies
Vernon
Ysander

Figure H-6. Publication Bias Test (Trim and Fill)



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.42983	1.11057	1.84087	1.41543	1.06277	1.88512	8.21613
Adjusted values	0	1.42983	1.11057	1.84087	1.41543	1.06277	1.88512	8.21613

Sensitivity Analyses (Key Question 4)

ICD Discharge while Driving

Figure H-7. Random-effects Meta-analysis

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Akayama	0.081	0.055	0.119	-11.382	0.000
Trappe	0.047	0.024	0.091	-8.324	0.000
Conti	0.007	0.000	0.099	-3.517	0.000
Finch (1997)	0.037	0.012	0.109	-5.538	0.000
Craney and Powers	0.042	0.014	0.121	-5.316	0.000
Finch	0.071	0.018	0.245	-3.495	0.000
	0.057	0.038	0.084	-12.894	0.000

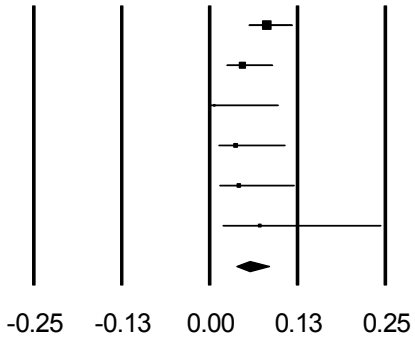


Figure H-8. Removal of One Study at a Time

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Akayama	0.044	0.027	0.069	-12.262	0.000
Trappe	0.068	0.048	0.094	-14.404	0.000
Conti	0.065	0.048	0.087	-16.313	0.000
Finch (1997)	0.066	0.048	0.089	-15.689	0.000
Craney and Powers	0.065	0.048	0.088	-15.753	0.000
Finch	0.062	0.046	0.085	-16.238	0.000
	0.063	0.047	0.084	-16.608	0.000

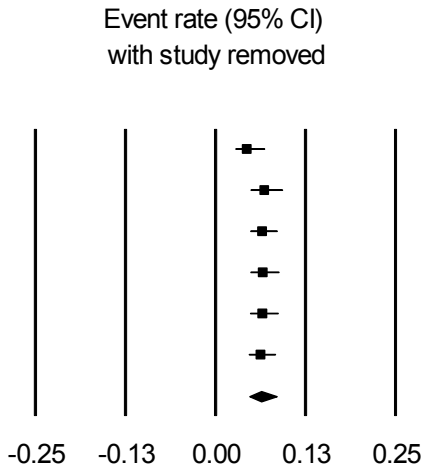


Figure H-9. Cumulative FEMA (highest weight study first)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Akayama	0.081	0.055	0.119	-11.382	0.000
Trappe	0.071	0.050	0.098	-14.031	0.000
Finch (1997)	0.067	0.048	0.092	-15.044	0.000
Conti	0.065	0.047	0.089	-15.361	0.000
Craney and Powers	0.062	0.046	0.085	-16.238	0.000
Finch	0.063	0.047	0.084	-16.608	0.000
	0.063	0.047	0.084	-16.608	0.000

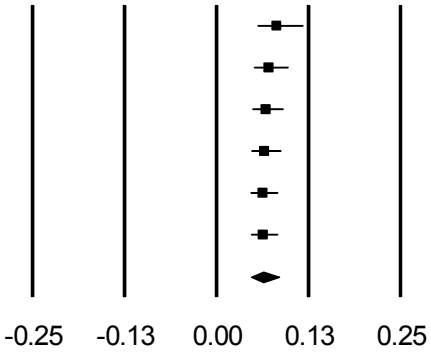


Figure H-10. Cumulative FEMA (most recent study first)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Akayama	0.081	0.055	0.119	-11.382	0.000
Trappe	0.071	0.050	0.098	-14.031	0.000
Conti	0.068	0.049	0.095	-14.366	0.000
Finch (1997)	0.065	0.047	0.089	-15.361	0.000
Craney and Powers	0.062	0.046	0.085	-16.238	0.000
Finch	0.063	0.047	0.084	-16.608	0.000
	0.063	0.047	0.084	-16.608	0.000

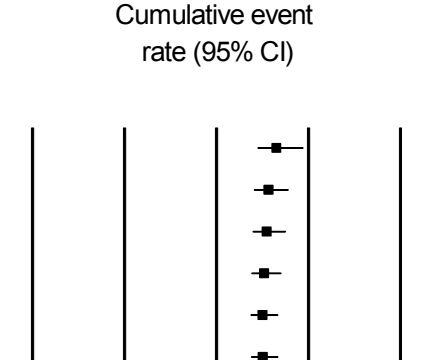
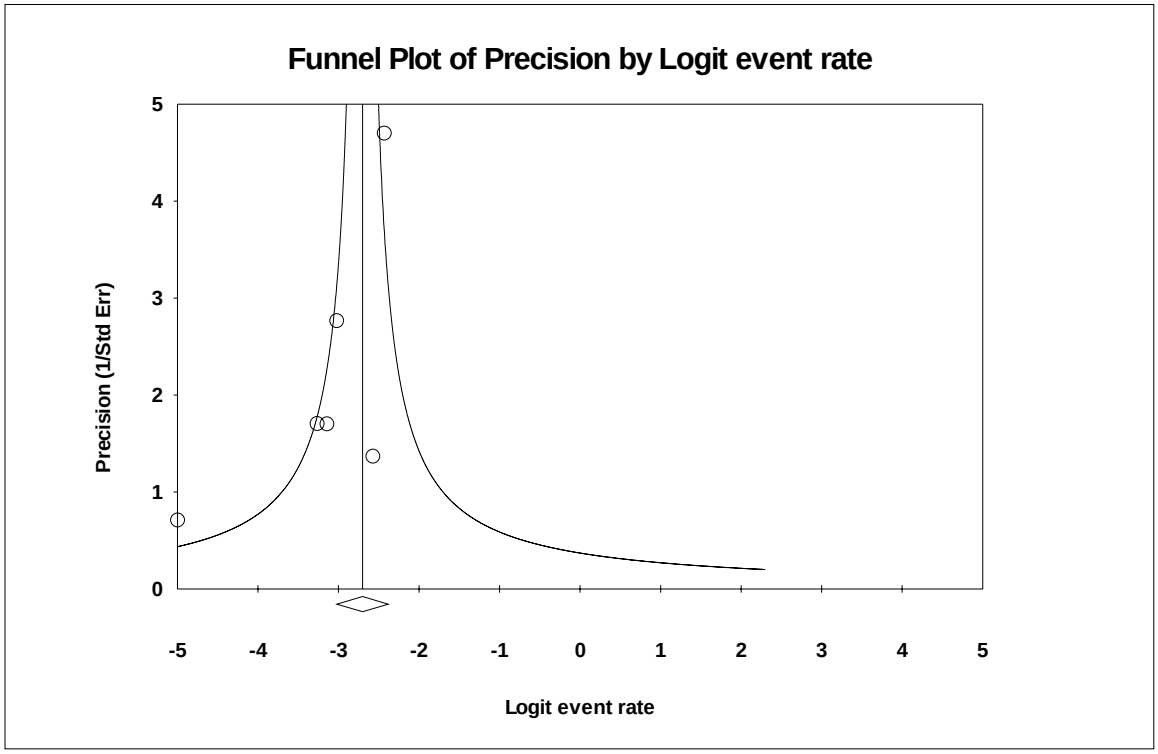


Figure H-11. Publication Bias Test (Trim and Fill)



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.06287	0.04651	0.08449	0.05654	0.03760	0.08419	6.51619
Adjusted values	0	0.06287	0.04651	0.08449	0.05654	0.03760	0.08419	6.51619