Evidence Report

2010 Update: Diabetes and Commercial Motor Vehicle Driver Safety

Federal Motor Carrier Safety Administration

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Prepared for:

Federal Motor Carrier Safety Administration
U.S. Department of Transportation

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Policy statement

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Executive Summary

Findings

Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

General Answer to Key Question 1: Yes (With Qualifications)

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

1. **A paucity of data from studies that enrolled Commercial Motor Vehicle (CMV) drivers with diabetes precludes one from determining whether CMV drivers with diabetes are at increased risk for a motor vehicle accident.**

   A single study (Overall Quality=Moderate) evaluated crash risk among CMV drivers with diabetes compared with comparable CMV drivers without diabetes. This was the only *included study to specifically assess crash risk among CMV drivers with diabetes. Because it was not a high-quality study with non-replicated findings, one cannot draw an evidence-based conclusion regarding possible increased crash risk for CMV drivers with diabetes.*

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

   Data examining crash risk in individuals with diabetes found that the magnitude of increased crash risk was small and not statistically significant (Risk Ratio=1.126; 95% CI: 0.847–1.497; P=0.415). (Stability of Estimate of Risk Ratio: Weak).

   Significant differences in diabetes related crash risk were found in a separate analysis performed with the studies divided by origin. Studies conducted in the US found a significantly increased crash risk in drivers with diabetes when compared to drivers without diabetes (Risk Ratio=1.284; 95% CI: 1.124—1.466; P<0.0001). Studies conducted in non-US countries did not demonstrate an increased diabetes related crash risk (Risk Ratio=1.035; 95% CI: 0.720-1.487; P=0.854).

   Fifteen studies (Overall Quality=Low-to-Moderate) compared crash risk among drivers with diabetes (cases) and drivers without diabetes (controls). Evidence base outcome data were presented as a Risk Ratio (RR), which is the ratio of crash incidence among drivers with diabetes and crash incidence among comparable drivers without diabetes. An RR value above 1.00 indicates that drivers with diabetes are at a higher risk for crash than drivers without diabetes.

   Quantitative analysis of the studies found heterogeneity (I^2 =94.256; Q=243.712, P<0.0001). A random effects meta-analysis found that crash risk for drivers with diabetes was 1.126 (95% CI: 0.847–1.497) times greater than the crash risk for drivers without diabetes. The RR did not reach statistical significance.

   A subgroup analysis that categorized studies according to whether or not they were conducted in the US was performed specifically for the 2010 update. The need for this subgroup analysis became apparent when it was realized that many non-US countries employ a three-year license review criterion for individuals with insulin-dependent diabetes mellitus (IDDM), the potential consequence of which being the removal of individuals with diabetes who are at the greatest risk for motor vehicle crash from the driving population. Removing these individuals would lessen or nullify any potential crash risk that having diabetes might present. Because the US does not have a comparable license review process for IDDM drivers (meaning that these individuals remain in the driving population) the observed crash risk may be higher in the US. Subgroup analyses support this suggestion. The RR for the US vs. Non-US subgroup analyses suggested that the crash risk was larger in the US (1.284; 95% CI=1.124-1.466 P<0.0001) than for individuals with diabetes in Non-US countries (1.035; 95% CI: 0.720-1.487;

P=0.854. This risk was even greater in the analysis of insulin-treated drivers compared with drivers who use oral medications and/or diet to control their condition (US subgroup: 2.753; 95% CI: 1.537—4.930; P=0.001; Non-US Subgroup: 1.036; 95% CI: 0.682—1.573; P=0.868).

3. **Whether drivers with type 1 or type 2 diabetes are overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**

Four studies (Overall Quality=Moderate) compared the prevalence of drivers with diabetes among a cohort of drivers who had experienced a crash with the prevalence of drivers with diabetes among a cohort of drivers who had not experienced a crash. Evidence base outcome data were presented as Odds Ratios (OR), which reflects the ratio of the odds of having diabetes and having been in a crash relative to the odds of having diabetes and not having been in a crash. An OR above 1.00 indicates that drivers with diabetes are at a higher risk for crash than non-diabetics (e.g. the odds of having diabetes in the crash group is higher than the odds of having diabetes in the non-crash group).

Homogeneity testing found that the findings of the four included studies differed significantly. The small size of the evidence base precluded the use of meta-regression analysis to explain the heterogeneity. Random effects meta-analysis was then used to pool the heterogeneous data. The magnitude of effects shows a slight increase in crash rates of drivers with diabetes when compared to those without diabetes (OR=1.052, 95% CI: 0.970-1.141; P=0.220) but the difference was insignificant. After controlling for the country in which the study was conducted, the US ORs are larger but still insignificant (OR=1.684, 95% CI: 725-3.911, P=0.225), while non-US ORs are not significant (OR=1.047, 95% CI: 0.966-1.136, P=0.265).

4. **Whether the subgroup of drivers with diabetes that is controlled by insulin is overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.**

The studies included in the previous analysis also attempted to determine whether drivers with insulin treated diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. Because the data were homogeneous, they were pooled using fixed effects meta-analysis, which found that drivers with insulin controlled diabetes tend to be overrepresented among samples of drivers who have experienced a crash: this result was not statistically significant (OR=1.212; 95% CI: 0.939–1.563, P=0.139). Controlling for the country in which the study was conducted does not change the findings (US Subgroup: OR=2.324; 95% CI: 0.554–9.741, P=0.249; Non US Subgroup: OR=1.186, 95% CI: 0.916-1.536, P=0.196). We conclude that it currently remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data is required before an evidence-based conclusion about whether drivers with diabetes controlled by insulin are overrepresented among populations of drivers who have crashed can be reached.

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

General Answer to Key Question 2: Yes (With Qualifications)

None of the included studies examined the effects of hypoglycemia on simulated driving ability, cognitive function, or psychomotor function in a group of CMV drivers with diabetes. All of the included studies examined the effects of hypoglycemia in individuals with type 1 diabetes – no individuals with type 2 diabetes were enrolled in any included study. Even if current interstate restrictions on CMV drivers with insulin-treated diabetes are lifted, non-insulin-treated individuals with type 2 diabetes will still constitute the vast majority of CMV operators who have the disorder. Consequently, the degree to which the findings of the included studies (particularly findings related to specific driving skills) can be generalized to CMV operators is unclear.

1. **Hypoglycemia has a significant deleterious effect on the driving ability of some individuals with type 1 (or IDDM) when measured using a driving simulator (Strength of Evidence: Moderate).**

- **Due to a paucity of data (three studies), no attempt was made to determine a quantitative estimate of the relationship between deterioration in driving competence and blood glucose levels.**

Three studies (Overall Quality=Moderate) assessing the effects of induced hypoglycemia on simulated driving ability found that driving ability was impaired during hypoglycemia across several variables. There is little agreement on which aspects of driving ability are most vulnerable or at what levels impairments manifest.

2. **Hypoglycemia has a significant deleterious effect on the cognitive and psychomotor function of individuals with type 1 (or IDDM) as measured by a number of different tests of cognitive function (Strength of Evidence: Moderate).**
   - **Because of the variety of cognitive and psychomotor function tests used, variable testing conditions, and variable blood glucose levels at which testing was performed, no attempt was made to determine a quantitative estimate of the relationship between functional loss and blood glucose levels.**

Twenty-four (Overall Quality=Low-to-Moderate) studies assessed the effects of insulin-induced hypoglycemia on cognitive and psychomotor function. These studies consistently demonstrated that moderate hypoglycemia (blood glucose levels in the region of 2.5-3.0 mmol/L[45–54 mg/dl]) had an acute deleterious effect on the ability of some *individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks: others did not appear to be affected at these levels. Still others appeared to be unaware that they were hypoglycemic and/or tended to underestimate the impact that hypoglycemia was having on cognitive and psychomotor function. At the present time no comparable data sets are available for individuals who do not require insulin to control their diabetes.*

Key Question 3: What risk factors are associated with an increased incidence of severe hypoglycemia, and what is the incidence of severe hypoglycemia with different treatments and treatment modalities (e.g., use of injectable, non-insulin drugs such as Byetta)?

General Answer to Key Question 3: Unclear

The primary aim of treatments for individuals with diabetes is to control blood glucose levels at near normal levels because maintaining tight control reduces the risk for developing the long-term complications associated with type 1 and type 2 diabetes.[1-4] Because the primary limiting factor for attaining tight blood glucose level control is hypoglycemia, much effort has been exerted in the development of new drugs, treatment regimens, and treatment delivery methods that allow tight control while minimizing hypoglycemia risk.

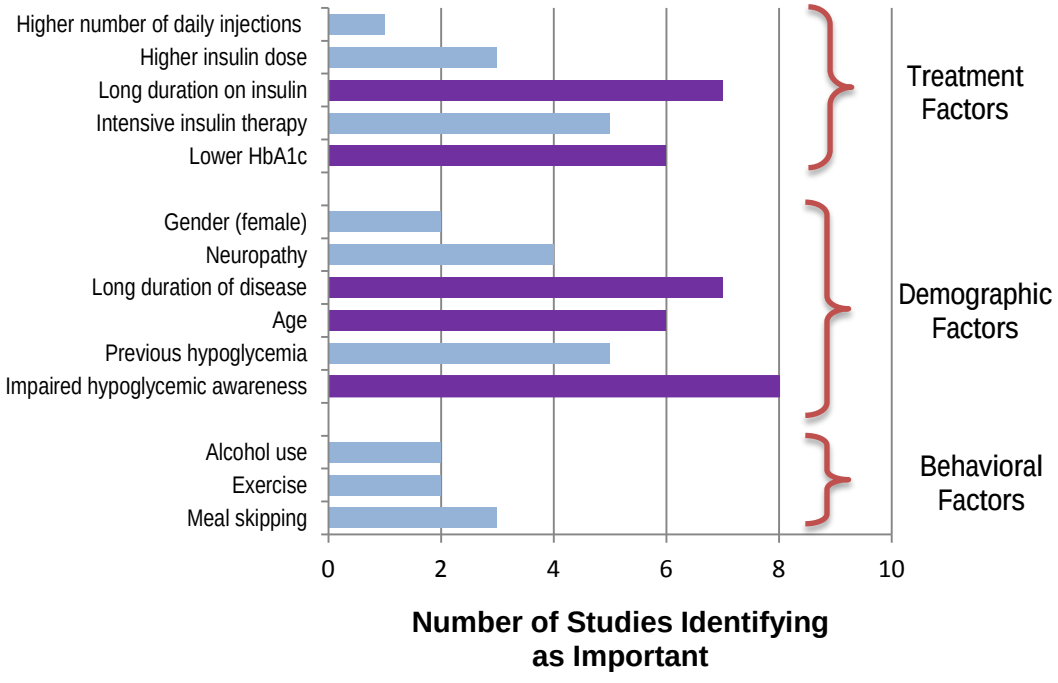
This section is divided into three subsections:

1. Subsection 1 is a high-level summary of studies that attempted to determine which treatment-related factors are associated with an increased risk for severe hypoglycemia in order to highlight their behavioral, demographic, and treatment-related risk factors.
2. Subsection 2 is a high-level summary of available systematic evidence reviews and meta-analyses that provide data on the incidence of severe hypoglycemia associated with specific treatment options in order to determine whether there is any evidence that some treatment options, treatment regimes, or treatment delivery methods present less of a risk for the development of severe hypoglycemia than others. Treatment options considered are limited to those identified in the Background section of this evidence report and include only treatments that have US Food and Drug Administration (FDA) approval for marketing. Experimental treatments, or those no longer available, are not considered.
3. Subsection 3 provides a high-level summary of risks associated with new injectable non-insulin based medications currently used to treat diabetes, including exenatide (Byetta®) and liraglutide (Victoza®).

Summary of Findings Regarding Risk Factors Associated with Incidence of Severe Hypoglycemia

A number of risk factors have been repeatedly shown to be associated with an increased incidence of severe hypoglycemia (see summary Figure, below).

Factors Frequently Associated with Increased Risk for Severe Hypoglycemia



Summary of Findings Regarding Treatment Factors Associated with Severe Hypoglycemia

A high-level overview of systematic evidence reviews regarding various treatment-related factors that have been shown to be associated with either increased are decreased incidence of severe hypoglycemia was provided. Key findings included:

- Differences in occurrence of severe hypoglycemia in type 1 and type 2 patients taking short-acting insulin analogues compared with regular human insulin was minimal. There were significant reductions in the rate of severe hypoglycemia with the use of long-acting analogues compared with regular human insulin.
- Published meta-analyses revealed mixed results with regard to continuous subcutaneous insulin injection (CSII) when compared with multiple daily injections in reducing the incidence of severe hypoglycemia. However, study results suggest a trend toward a reduction in severe hypoglycemia in type 1 patients using CSII compared to multiple daily injections.
- Two recent meta-analyses clearly show the benefit of tight/intensive glycemic control in reducing long-term complications in patients with type 2 diabetes. Incidence of severe hypoglycemic events is also significantly increased.
- Self-monitoring of blood glucose (SMBG) in non-insulin treated patients with type 2 diabetes was found to be associated with significant increases in the rate of hypoglycemia.

Summary of Findings Regarding Injectable, Non-Insulin Drugs

Trials published to date show a small but significant risk of hypoglycemia when exenatide is used in conjunction with a sulphonylurea. Hypoglycemia risk is similarly raised when the gliptins (DPP4 inhibitors) or liraglutide are used with sulphonylureas.

According to the Driver & Vehicle Licensing Agency (DVLA) in the United Kingdom (UK), the increased risk of hypoglycemia from exenatide, liraglutide, or gliptins / sulphonylureas combination therapy is such that it is considered

a potentially high-risk treatment for drivers holding Group 2 (Large Goods Vehicle [LGV]) or Passenger Carrying Vehicle ([PCV]) licenses and that individual assessment of these drivers is required. Group 2 drivers are required to notify the DVLA if they have diabetes treated with tablets. If they use exenatide, liraglutide, or a gliptin they are only required to notify DVLA if this is in combination with a sulphonylurea due to the increased hypoglycemia risk.

Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

General Answer to Key Question 4: Unclear

Our evidence-based conclusions on the effectiveness of hypoglycemia awareness training are presented below.

1. **Awareness training programs (i.e., Blood Glucose Awareness Training [BGAT] and HyPOS) improve the ability of individuals with type 1 diabetes to improve the accuracy in estimating their blood glucose levels (Strength of Evidence: Moderate).**

   A total of six prospective studies (5 randomized controlled; 1 non-randomized controlled) (Overall Quality= Moderate) that enrolled a total of 334 individuals with type 1 diabetes evaluated the effectiveness of BGAT or a reduced training program called HyPOS in improving the accuracy of self-determined blood glucose estimates.

   Qualitative assessment of the available data found that currently available evidence consistently demonstrated that BGAT or HyPOS improves the ability of individuals with type 1 diabetes to improve the accuracy of their blood glucose level estimates.

2. **A paucity of consistent evidence precludes a determination from being made concerning whether awareness training (BGAT or HyPOS) is effective in reducing the incidence of severe hypoglycemia.**

   Three small (Overall Quality=Moderate) studies that enrolled a total of 253 individuals with type 1 diabetes presented data on the incidence of severe hypoglycemia following exposure to awareness training. Results were inconsistent, with one study finding a benefit while the other two did not. Because the inconsistencies in the findings could not be explained, it remains unclear whether exposure to BGAT or HyPOS results in measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

Preface

Organization of Report

This evidence report contains five major sections: 1) Background, 2) Regulation and Guidelines for CMV Drivers, 3) Methods, 4) Synthesis of Results, and 5) Conclusions. These major sections are supplemented by extensive use of appendices.

In Section 1: Background, we provide background information about diabetes, including details about the epidemiology of the condition, treatment, treatment side effects, and the potential impact on driver safety. In Section 2: Regulation and Guidelines for CMV Drivers, we examine the diabetes mellitus standards and guidelines established by the United States and other countries regarding diabetes and CMV drivers. We also highlight relevant information from individual states. In Section 3: Methods, we provide key methodological details, including how we identified and analyzed information for this report. This section covers the key questions addressed, details of literature searching, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesis of clinical study results. Section 4: Synthesis of Results provides the key findings of this report and 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, qualitatively and quantitatively (using meta-analysis). Each section in the Synthesis of Results section closes with our conclusions, which are based on our assessment of the available evidence. Section 5: Conclusions briefly summarizes the answers to each of the key questions addressed in this report. A number of appendices are also included.

Scope

This report is an update to a systematic evidence review titled "Diabetes and Commercial Motor Vehicle Driver Safety (Expedited Review)" dated September 8, 2006. This update evaluated the same questions and used the same eligibility criteria, with the exception of slightly revised criteria for Key Question 2 (details of the modified criteria are outlined below). The updated literature search was conducted through November 4, 2010.

The primary focus of the updated report (like that of the original report) is on the risks to driver safety from the acute risks associated with diabetes mellitus (e.g., hypoglycemia). This report does not address driver safety issues related to chronic complications of diabetes (e.g., diabetic nephropathy, neuropathy, retinopathy, and/or cardiovascular conditions resulting from the long-term complications of diabetes).

Four key questions addressed in the original report (2006) and this updated evidence report, are as follows:

Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

In addressing this question we examine the relationship between hypoglycemia and the following direct and indirect outcome measures:

a. Simulated driving performance (indirect)

b. Driving-related cognitive and psychomotor performance (indirect)

Key Question 3: What risk factors are associated with an increased incidence of severe hypoglycemia, and what is the incidence of severe hypoglycemia with different treatments and treatment modalities (e.g., use of injectable, non-insulin drugs such as Byetta®)?

Potential factors to be assessed in addressing this question include the following:

a. Mechanism of glycemic control (insulin, first generation sulfonylureas, second generation sulfonylureas, meglitinides, and other hypoglycemic drugs used to control blood glucose levels)
b. Route of insulin administration (inhaled, subcutaneous injection, pump)

Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

The effects of the chronic complications of diabetes mellitus on driving ability are beyond the scope of the present evidence report. However, these complications will be discussed in later proceedings.

Section 1: Background

More work-related fatalities in the U.S. result from transportation incidents than from any other event (http://www.bls.gov/iif/oshwc/cfoi/cfch0006.pdf). Highway incidents alone accounted for one out of every four fatal work injuries in 2007, the most current year of data on record (U.S. Bureau of Labor Statistics [BLS], 2009). Workers in the trucking industry experienced the second- highest fatality rate in 2007, accounting for 16.9 percent of all worker deaths.

According to statistics from the U.S. Department of Transportation (DOT) (http://ai.volpe.dot.gov/CrashProfile/n_overview.asp), there were 110,619 crashes involving a large truck in 2009 (DOT, 2010). Of these, 42,774 were crashes that resulted in an injury to at least one individual, for a total of 59,259 injuries and 3,380 fatalities. These numbers are down from the year before, when in 2008, 134,021 large trucks were involved in an accident, resulting in 71,524 injuries and 4,245 fatalities.

Although the total number of transportation incidents continues to drop every year, transportation incidents still account for the majority of work-related fatalities. Of the four types of transportation incidents identified by the BLS, highway incidents continue to account for more than 50 percent of all transportation incidents (Table 1).

Table 1: Number of Fatal Occupational Injuries, Transportation Incidents and Highway Incidents

	Work-Related Fatalities		Transportation Incidents		Highway Incidents	
	Total	Percent	Total	Percent of Work-Related Fatalities	Total	Percent of Transportation Incidents
2009	4,340*	100	1,682*	39	882*	52
2008	5,214	100	2,130	41	1,215	57
2007	5,657	100	2,351	42	1,414	60
2006	5,840	100	2,459	42	1,356	55

Source: BLS, 2010
* Preliminary annual data for 2009

1.1. Diabetes Mellitus

Diabetes mellitus is a group of diseases characterized by abnormally high levels of blood glucose. These high blood glucose levels result from defects in insulin secretion, insulin action, or both. Diabetes mellitus is typically classified as type 1 or type 2 diabetes. Another less common form of diabetes is gestational diabetes, a form of diabetes that occurs in some women during pregnancy.

Type 1 diabetes was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Type 1 diabetes may account for 5 to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for type 1 diabetes than for type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes.

Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90 to 95 percent of all diagnosed cases of diabetes. Risk factors for type 2 diabetes include older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes.

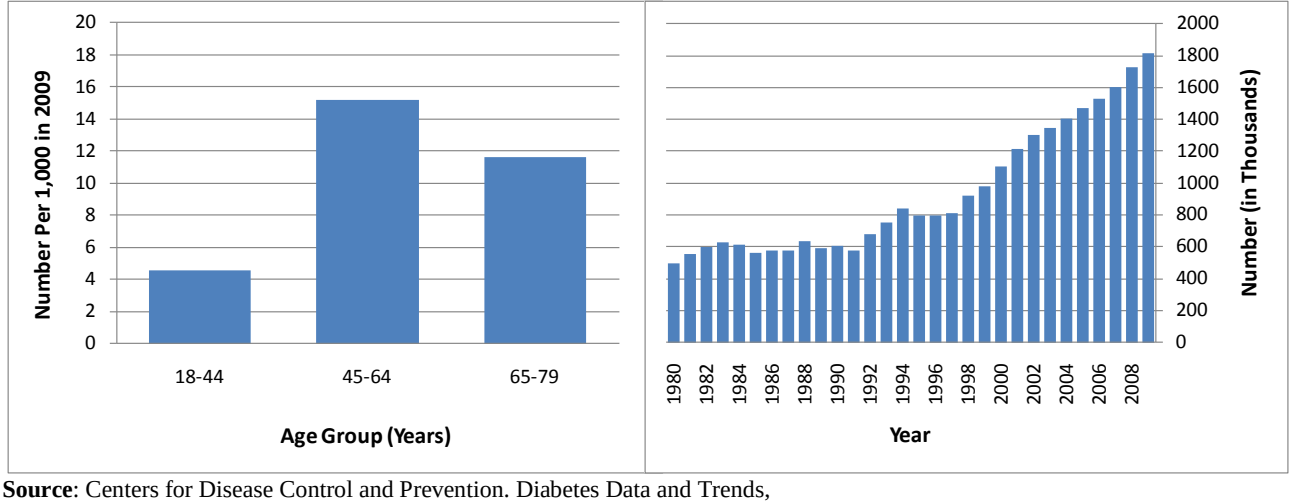
1.2. Epidemiology Data for Diabetes in the United States

1.2.1. Prevalence and Incidence of Diabetes Mellitus

According to the most recent statistics from the National Institute of Diabetes and Digestive and Kidney Diseases, an estimated 23.6 million people in the United Sates have diabetes. Of these, 17.9 million people have been diagnosed and an estimated 5.7 million people remain undiagnosed. (http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#allages). The incidence of new cases of diabetes among individuals aged 18 years or older in the United States was estimated to be 1.6 million in 2007.

Figure 1A displays the number of new cases of diagnosed diabetes per 1,000 U.S. adults aged 18 to 79 years. In the year 2009, there were about 4.6 new cases per 1,000 people aged 18–44 years; 15.2 new cases among people aged 45–64 years; and 11.6 new cases among people aged 65–79 years. Figure 1B displays the total number of newly diagnosed cases of diabetes (aged 18-79 years) in the United States each year from 1980 through 2009. As can be seen in Figure 1B, from 1980 through 2009, the number of adults in the United States aged 18–79 with newly diagnosed diabetes more than tripled from 493,000 in 1980 to more than 1.8 million in 2009. The number of new cases of diabetes has increased sharply since the early 1990s.

Figure 1: Incidence of Diagnosed Diabetes (1A: Incidence per 1,000 by Age Group in 2009; 1B: Annual Number (in Thousands) Among Adults Aged 18–79 Years, United States, 1980–2009)



Source: Centers for Disease Control and Prevention. Diabetes Data and Trends, http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm

1.2.2. Mortality

According to the National Center for Health Statistics, in 2005, diabetes contributed to a total of 233,619 deaths, and was the primary underlying cause of 74,219 deaths. The 2010 National Vital Statistics Report presents data through 2007.[5] In 2007, diabetes was the seventh-leading cause of death, contributing to 71,382 total deaths. This was a 3.4 percent decrease from reported values in 2006. Mortality from diabetes also increases substantially with age. Annual mortality per 100,000 in the U.S. population in 2007 is presented below by age group:

- **15–24 years**: 0.4 (total number: 168)
- **25–34 years**: 1.5 (total number: 610)
- **35–44 years**: 4.6 (total number: 1,964)
- **45–54 years**: 13.1 (total number: 5,763)
- **55–64 years**: 34.6 (total number: 11,304)

- **65–74 years**: 78.1 (total number: 15,112)
- **75–84 years**: 162.7 (total number: 21,189)
- **85+ years**: 276.2 (total number: 15,227)

The number of U.S. deaths from diabetes by gender and race in 2007 is presented below.

- **Male**: 35,478
- **Female**: 35,904
- **White**: 56,390
- **Black**: 12,459
- **Hispanic**: 6,417

1.2.3. Risk Factors for Diabetes

Risk factors for diabetes have been well established. Some of the most common risk factors that are most relevant to the CMV driver population include the following:

- Age greater than 45 years
- Excess body weight (especially around the waist)*
- Family history of diabetes
- HDL cholesterol under 35 mg/dL
- High blood levels of triglycerides, a type of fat molecule (250 mg/dL or more)
- High blood pressure (greater than or equal to 140/90 mmHg)
- Impaired glucose tolerance
- Low activity level (exercising less than 3 times a week)
- Metabolic syndrome

**A summary of information pertinent to this risk factor in CMV drivers is presented below.*

1.2.3.1. Obesity in CMV Drivers

The prevalence of obesity in the United States has increased steadily, from 22.9 percent in 1994 to 34.3 percent in 2006 (among adults aged 20 and over).[6] Obesity is defined as having a body mass index (BMI; unit kg/m^2) of 30 and above; extreme obesity is defined as having a BMI of 40 and above. The prevalence of extreme obesity in the United States has increased from 2.9 percent in 1994 to 5.9 percent in 2006 – a three-fold increase.[6] The rate of obesity among CMV drivers tends to be higher than the obesity rate in the general population. In a 1993 study by Korelitz et al., 40 percent of CMV drivers participating in the study were classified as overweight (BMI between 25 and 30) and 33 percent were classified as obese.[7] This may have implications for CMV driver safety and health. For instance, Stoohs et al. (1994) found that obese CMV drivers had a two-fold risk of having an accident per 10,000 miles in the last five years, compared with non-obese CMV drivers.[8]

As noted above, obesity is a leading risk factor for the development of diabetes mellitus. Given that evidence points to a higher incidence of overweight and obesity in CMV drives, one might also expect to find a higher prevalence of diabetes (or early stage diabetes). In a study by Martin et al. (2009), higher-weight participating CMV drivers were more likely to suffer from hypertension, hyperlipidemia (high cholesterol and triglycerides) or diabetes, compared with lower-weight CMV drivers.[9] A summary of findings related to obesity among CMV drivers is presented in Table 2.

Table 2: Summary of Study Findings Related to Obesity and High Blood Pressure among CMV Drivers

Author(s)	Year	Country	Population Characteristics	Study Objective	Results/Findings
Martin et al.[9]	2009	U.S.	2,950 male truck drivers, who (1) Had received a DOT physical in 2004 (2) Were eligible for health benefits in the year following their physical (3) Had a BMI (kg/m^2) ≥18.5	To quantify health care costs of employees (truckers) across categories of normal weight, overweight, and obese. To determine the impact of BMI levels on diabetes, hyperlipidemia, and hypertension prevalence.	• 41% of participants had hypertension, 21% had hyperlipidemia, and 16% had diabetes. The higher weight categories had a greater prevalence of each of these three conditions ($p<0.001$ for each). For example, the prevalence of hypertension was 21%, 31%, and 51% across the normal weight, overweight, and obese weight categories, respectively ($p<0.001$).
Stoohs et al.[8]	1994	U.S.	90 truck drivers (93% male), aged 36.5±8.7 years; BMI 29.2±6.6 kg/m^2	To evaluate whether a non-selected group of long-haul truck drivers with significant breathing abnormalities during sleep may be at risk for causing more traffic accidents than drivers without the syndrome.	• Obese drivers had a mean of 0.1 accidents/ 10,000 miles within the last 5 years, compared with a mean of 0.045 accidents/ 10,000 miles within the last 5 years in non-obese drivers ($p<0.03$). • Analysis of questionnaire items showed that obese truck drivers were significantly sleepier than non-obese truck drivers. • Obese truck drivers reported falling asleep unintentionally more often than non-obese truck drivers (mean 2.76±0.90 vs. 2.40±0.82; $p<0.05$).
Korelitz et al.[7]	1993	U.S.	2,945 truck drivers participating in a voluntary truck show	To provide a descriptive summary of personal characteristics, health status, and health interests reported by truck drivers who attended a trucker trade show.	• 33% of truck drivers were obese (BMI≥30), and an additional 40% were overweight (BMI ≥25 but <30). • 66% of truck drivers who hadn't received a diagnosis of hypertension had a blood pressure of 140/90 or above. • 49% of truck drivers who hadn't received a diagnosis of hypertension had a blood pressure of 160/95 or above.
Marcinkiewicz et al.[10]	2010	Poland	570 road transport drivers	To investigate obesity, hypertension and carbohydrate metabolism disorders among road transport drivers.	• Overweight was recorded in 62.6% of drivers (BMI≥25), and 17.4% of drivers were obese (BMI≥30). • Hypertension (≥140/90 mmHg) was noted in 36.7% of drivers, but, according to medical records, hypertension was diagnosed in just 4.9% of drivers. • Risk for hypertension in overweight subjects was 4.23-fold as high as in those with normal body weight (95% CI: 2.82–6.36). • Hyperglycemia was found in 47.5% of drivers; 50% of overweight drivers and 62.5% of obese drivers had hyperglycemia. 65.5% of drivers with overweight/obesity and hypertension had hyperglycemia, compared with 34.8% of drivers at normal weight and blood pressure.
Dahl et al. [11]	2009	Denmark	2,175 male truck drivers; mean age 39.4 years (range: 20-59 years)	To elucidate the disease pattern among male professional long-haul truck drivers in Denmark.	• Compared with the working population at large, long-haul and other truck drivers had a statistically significant elevated risk for being hospitalized for obesity (SHR*: 254, 95% CI: 127–454) and diabetes mellitus (SHR: 140, 95% CI: 104–185).

* SHR: standardized hospitalization ratio

1.3. Economic Burden of Diabetes

The economic burden of diabetes on the U.S. economy is significant. According to a study commissioned by the American Diabetes Association and performed by the Lewin Group[12], the direct and indirect expenditures attributable to diabetes in 2007 were approximately $174 billion. Estimates of direct medical expenditures attributed to diabetes totaled $116 billion, comprising $27 billion for diabetes care, $58 billion to treat diabetes-related chronic complications, and $31 billon in excess general medical costs. Attributable indirect expenditures resulting from lost workdays, reduced productivity, early mortality, and disability due to diabetes totaled $58 billion. U.S. health expenditures for the health care components included in the study were estimated at $1 trillion, of which about $205 billion was incurred by people with diabetes, reflecting $1 of every $5 health care dollars. For the cost components analyzed in the study, people with diabetes in 2007 had health care expenditures 2.3 times higher ($11,744 vs. $5,095) than expenditures for the population of the same age and sex without diabetes.

1.4. Treatment of Diabetes Mellitus

Treatments for diabetes mellitus aim to maintain blood glucose levels near normal (euglycemia) at all times. Because type 1 and type 2 diabetes have different etiologies, the treatments for these disorders differ. A lack of insulin production by the pancreas makes type 1 diabetes particularly difficult to control. Treatment requires a strict regimen that typically includes a carefully calculated diet, planned physical activity, home blood glucose testing several times a day, and multiple daily insulin injections. Treatment for type 2 diabetes typically includes diet control, exercise, home blood glucose testing, and, in some cases, oral medication and/or injections of insulin or non-insulin.

Approximately 40 percent of people with type 2 diabetes require insulin injections. Among adults with diagnosed diabetes of either type, 14 percent take insulin only, 13 percent take insulin and oral medication, 57 percent take oral medication only, and 16 percent do not take insulin or oral medication.[13] The percentage of diabetics using injectable, non-insulin based drugs is not known.

As stated above, currently available treatment options for individuals with diabetes include insulin (required by all individuals with type 1 diabetes and up to 40 percent of those with type 2 diabetes) and a number of different classes of oral agents. Table 3, Table 4, and Table 5 provide a list of oral agents, combined oral agents, and insulin preparations (and non-insulin injectable drugs), respectively, that are currently used by individuals with diabetes in the United States. Included in the tables are links to Websites with relevant labeling information. Accurate and publicly available product labeling information is required by FDA for any drug to be marketed in the United States. Product labeling provides details on the active agent, its dosing regimen, and its indications and contraindications, and provides details of adverse events that have occurred (or may occur) among individuals using the medication.

Table 3: Oral Treatments for Diabetes in the United States

Class	Generic	Trade Names	Type	Primary Action	Typical Dosage	Link to Labeling Information*	Blood Glucose Most Affected	Greatest Risk for Hypoglycemia
Sulfonylureas – first generation	Acetohexamide	Dymelor®	2	This drug has been discontinued in the United States				
	Chlorpropamide	Diabinese® Glucamide®		Increases insulin production in the pancreas	100 to 500 mg/twice a day; max, 750 mg/day	http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH000069	Fasting and postprandial	Nocturnal, fasting, 4 to 6 hours after meals
	Tolazamide	Tolinase®			100 to 1,000 mg/day in divided doses; max 1 g/day	www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682482.html		
	Tolbutamide	Orinase® Tol-Tab ®			.25 to 2 g/day in divided doses; max 3 g/day	www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682481.html		
Sulfonylureas – second generation	Glimepiride	Amaryl®	2	Increases insulin production in the pancreas	1 to 8 mg/day; max 8 mg/day	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000981	Fasting and postprandial	Nocturnal, fasting, 4 to 6 hours after meals
	Glipizide	Glucotrol® Glucotrol® XL			2.5 to 20 mg/once or twice a day; max 40 mg/day; XL* 2.5 to 10 mg/once or twice a day; max 20 mg/day	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000833/		
	Glyburide	DiaBeta® Glynase® Micronase®			Glyburide: 1.25 to 5 mg/once or twice a day; max 20 mg/day Glynase: 0.75 to 12 mg/day; max 12 mg/day	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000833		
Biguanide	Metformin	Glucophage® Fortamet® Glumetza® Riomet®	2	Primarily decreases hepatic glucose production. Minor increase in muscle glucose uptake, which may improve insulin resistance	500 mg/day twice a day with meals, increase by 500 mg every 1 to 3 weeks, twice or three times a day; usually most effective at 2,000 mg/day; max 2,550 mg/day	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000974/	Fasting and postprandial	After exercise if prolonged and strenuous
Alpha-Glucosidase Inhibitors	Acarbose	Precose®	2	Slows absorption of complex carbohydrate from gastrointestinal (GI) tract	25 mg/day; increase by 25 mg mg/day every 4 to 6 weeks; max, split dose before meals (with first bite of food) 300 mg/day (150 mg/day for	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000980	Postprandial	When used in combination with insulin or other meds, it may cause excessive lowering of blood
	Miglitol	Glyset®				www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000074		

Class	Generic	Trade Names	Type	Primary Action	Typical Dosage	Link to Labeling Information*	Blood Glucose Most Affected	Greatest Risk for Hypogylcemia
					weight <60 kg)			sugar levels
Thiazolidine-diones	Pioglitazone	Actos®	2	Decreases insulin resistance, increasing glucose uptake, fat redistribution; minor decrease in hepatic glucose output; preserves cell function; decreases vascular inflammation	Initially 15 or 30 mg/day; max with food or without 45 mg for monotherapy, 30 mg for combination therapy	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001047	Fasting and postprandial	May cause hypoglycemia if taken in combination with other diabetes meds
	Rosiglitazone	Avandia®			Initially 4 mg/day in single or divided doses. Increase to 8 mg/day in 12 weeks, if needed; max 8 mg/day with or without food	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001051		
	Troglitazone	Withdrawn from market due to increased incidence of drug-induced hepatitis						
Meglitinides	Repaglinide	Prandin®	2	Increases insulin release from pancreas	New diagnosis or A1C > 8%, 1 to 2 mg, 15 to 30 minutes before each meal; increase weekly until results are obtained; max 16 mg/day	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000002	Postprandial	2 to 3 hours after meals
	Nateglinide	Starlix®	2	Increases insulin release from pancreas	60 to 120 mg/3 times a day, 1 to 30 minutes before a meal	www.accessdata.fda.gov/drugsatfda_docs/label/2008/021204s011lbl.pdf	Postprandial	2 to 3 hours after meals
Inhibitors of Dipeptidyl peptidase 4 (DPP-4)	Sitagliptin Phosphate	Januvia	2	Increases and prolongs active incretin levels, which increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner	25 mg, 50 mg, 100 mg once daily with or without food; max, 100 mg/day	www.ncbi.nlm.nih.gov/pmc/articles/PMC1994027/		When used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia
	Saxagliptin Phosphate	Onglyza			2.5 or 5 mg/once a day; can be taken with or without food	www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000515/		

Table 4: Combinations of Oral Agents for Treatment of Type 2 Diabetes

Agent	Classes	Primary Action	Typical Dosage	Blood Glucose Most Affected	Greatest Risk for Hypoglycemia
Glucovance® (glyburide and metformin)	Sulfonylureas and biguanide	Decreases hepatic glucose production and increases insulin secretion	Ratios of glyburide and metformin (in mg):1.25/250, 2.5/500, 5/500. Initial: 1.25/250 once or twice a day, increased every 2 weeks. Second line: 2.5–5/500 twice a day, increased every 1–2 weeks. Average dose 7.5/1,500. Max dose should not exceed 20 mg glyburide/2,000 mg metformin daily.	Fasting and postprandial	Nocturnal, fasting, 4 to 6 hours after meals
Metaglip® (glipizide and metformin)	Sulfonylureas and biguanide	Decreases hepatic glucose production and increases insulin secretion	Ratios of glipizide and metformin (in mg): 2.5/250, 2.5/500, 5/500. Initial: 2.5/250 once or twice a day, increased every 2 weeks. Second line: 2.5–5/500 twice a day, increased every 1– 2 weeks. Max dose should not exceed 20 mg glipizide/2,000 mg metformin daily.	Fasting	Nocturnal, fasting, 4 to 6 hours after meals
Avandamet® (rosiglitazone and metformin)	Thiazolidinedione and biguanide	Decreases hepatic glucose production, increases glucose uptake, decreases insulin resistance, and preserves -cell function	Ratios of rosiglitazone and metformin: 1 mg/500 mg, 2 mg/500 mg, 4 mg/500 mg, 2 mg/1,000 mg, 4 mg/1,000 mg twice a day; dosage individualized based on current therapy. Max, 8 mg/2,000 mg per day.	Fasting and postprandial	After exercise if prolonged and strenuous
Actoplus Met® (pioglitazone and metformin)	Thiazolidinedione and biguanide	Decreases hepatic glucose production, increases glucose uptake, decreases insulin	Ratios of pioglitazone and metformin: 15 mg/500 mg, 15 mg/850 mg.	Fasting and postprandial	After exercise if prolonged and strenuous
Avandaryl® (rosiglitazone and glimepiride)	Thiazolidinedione and sulfonylureas	Decreases insulin resistance and increases insulin secretion	Ratios of rosiglitazone and glimepiride: 4 mg/1 mg, 4 mg/1 mg.	Fasting and postprandial	Nocturnal, fasting, 4 to 6 hours after meals

Table 5: Injection Treatments for Diabetes in the United States

Generic	Trade Names	Type	Onset	Peak	Effective Duration	Maximal Duration	Comments	Labeling Links
Human Insulin								
Rapid Acting								
Aspart	NovoLog®	1 or 2	<15	1–2 hours	2–4 hours	3–5 hours	Should be taken just prior to or just after eating	www.nlm.nih.gov/medlineplus/druginfo/meds/a605013.html
Lispro	Humalog®	1 or 2	<15	1 to 3 hours	3-5 hours	4-6 hours	Should be taken just prior to or just after eating	www.nlm.nih.gov/medlineplus/druginfo/meds/a697021.html
Glulisine	Apidra®	1 or 2	<15	0.5–1 hour	3 hours	3 hours	Should be taken just prior to or just after eating	www.nlm.nih.gov/medlineplus/druginfo/meds/a607033.html
Short Acting								
Regular	Humulin® R Novolin® R	1 or 2	0.5-1 hour	2-4 hours	3-5 hours	8 hours	Best if taken 30 minutes before a meal	www.nlm.nih.gov/medlineplus/druginfo/meds/a682611.html
Intermediate Acting								
Lente	No longer available in the United States.							
NPH	Humulin® N Novolin® N ReliOn® (Wal-Mart)	1 or 2	2-4 hours	4-10 hours	10-16 hours	14-18 hours	Bedtime dosing minimizes nocturnal hypoglycemia	http://ndep.nih.gov/media/Drug_tables_supplement.pdf
Long Acting								
Ultralente	No longer available in the United States.							
Detemir	Levemir®	1 or 2	3-4 hours	50% in 3–4 hours, lasting up to 14 hours	5.7–23.2 hours	Dose depen-dent 5.7–23.2 hours	Cannot be mixed in same syringe with other insulins. Duration of action is dose dependent: 6 hours (0.1U/kg), 12 hours (0.2U/kg), 20 hours (0.4U/kg), 23 hours (0.8U/kg and 1.6U/kg)	http://ndep.nih.gov/media/Drug_tables_supplement.pdf
Insulin glargine	Lantus®	1 or 2	2-5 hours	No peak	24 hours	>24 hours		http://products.sanofi-aventis.us/lantus/lantus.html
Pre-mixed Insulins								
Lispro protamine, Insulin Lispro	Humalog® 75/25	1 or 2	<15	1-2 hours	10-16 hours	14-18 hours	75% NPL, 25% Lispro; should be taken just prior to or just after eating because of rapid onset. Caution because of name confusion with Humalog and Novolog	http://ndep.nih.gov/media/Drug_tables_supplement.pdf
NPH, Aspart	Novolog Mix® 70/30	1 or 2	<15	1-4 hours	10-16 hours	14-18 hours	70% NPH, 30% Aspart; should be taken just prior to or just after eating because of rapid onset. Caution because of name confusion with Humalog and Novolog	http://ndep.nih.gov/media/Drug_tables_supplement.pdf

Generic	Trade Names	Type	Onset	Peak	Effective Duration	Maximal Duration	Comments	Labeling Links
Isophane, Regular	Humulin® 70/30	1 or 2	0.5-1 hours	2-10 hours	10-16 hours	14-18 hours	70% NPH and 30% regular insulin	http://ndep.nih.gov/media/Drug_tables_supplement.pdf
Isophane, Regular	Novolin® 70/30	1 or 2	0.5-1 hours	2-10 hours	10-16 hours	14-18 hours	70% NPH and 30% regular insulin	http://ndep.nih.gov/media/Drug_tables_supplement.pdf
Lispro protamine, Insulin Lispro	Humulin® 50/50	1 or 2	No longer available					
Porcine or Beef Insulins								
Manufacturing of beef insulin for human use in the United States discontinued in 1998. From January 2006, pork insulin for human no longer manufactured or marketed in the United States								
Non-Insulins Glucagon-like Peptide-1 (GLP-1) agonist								
Exenatide	Byetta®	2	NA	2.1 hours	NA	NA	Initial: 5 mcg twice daily within 60 minutes prior to a meal; after 1 month, drug may be increased to 10 mcg twice daily (based on response)	www.nlm.nih.gov/medlineplus/druginfo/meds/a605034.html
Liraglutide	Victoza®	2	NA		NA	NA	Initial 0.6 mg/once a day; After first week, dose may be increased to 1.2 or 1.8 mg/day.	http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm198543.htm

1.4.1. Sulfonylureas

This was the first class of oral drugs available for the treatment of type 2 diabetes. Introduced in 1955, the sulfonylureas were the only blood sugar-lowering medications available in the United States until 1995. Sulfonylureas can be further classified into two groups or generations, based on their potency, duration of action, and drug interactions/side effects profiles. Regardless of generation, all sulfonylureas work in the same way to lower blood sugar; they stimulate beta cells in the pancreas to produce more insulin.

Second-generation sulfonylureas include glimepiride, glipizide, Glipizide ER, and glyburide. These latter drugs are all similarly effective in lowering blood sugar levels. However, some minor differences do exist among the second-generation sulfonylureas. Glipizide produces a more rapid lowering of blood sugar compared with glyburide. Glyburide, on the other hand, is more potent than glipizide. Glimepiride and glipizide ER are longer acting than the other two sulfonylureas.

1.4.2. Biguanides

Biguanides are used to treat type 2 diabetes. They work by decreasing the absorption of glucose by the intestines, decreasing the production of glucose in the liver, and by increasing the body's ability to use insulin more effectively. Metformin is currently the only drug in this category. When used as monotherapy, metformin does not cause hypoglycemia; thus metformin is classified as an antihyperglycemic agent rather than a hypoglycemic agent.

1.4.3. Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs) are given with meals and work by slowing the breakdown of the complex sugars into glucose. This results in delayed glucose absorption and lower blood sugars following meals. The AGIs may be used alone or in combination with other medications for diabetes. Glyset and Precose are the only available AGIs. Glyset is only indicated for combination therapy with a sulfonylurea, while Precose may be used with a sulfonylurea, metformin, or insulin. When used alone, AGIs do not cause hypoglycemia.

1.4.4. Thiazolidinediones

The thiazolidinediones are a relatively new group of drugs with a mechanism of action that differentiates them from most hypoglycemic agents. Unlike biguanides and sulfonylureas, thiazolidinediones decrease hepatic fat content and increase insulin sensitivity in muscle. These properties would seem to make the drugs particularly useful in patients with insulin-resistant type 2 diabetes, but no data are currently available to help identify the patients who would respond best to these drugs. Rosiglitazone and pioglitazone are currently approved in most countries for the treatment of hyperglycemia in patients with type 2 diabetes, either as monotherapy, or in combination with sulfonylureas or metformin. In the United States, both drugs have also been approved for use in combination with insulin, provided certain precautions are followed. The thiazolidinedione medication troglitazone (Rezulin) has been removed from the market in the United States and some European countries. Troglitazone has been shown to cause severe liver problems in a small number of people who take it. When used alone, thiazolidinediones do not cause hypoglycemia.

1.4.5. Meglitinides

Meglitinides are non-sulfonylurea insulin secretagogues that lower blood sugar levels by increasing the release of insulin from the pancreas. The drugs in this class are unique because they are relatively short-acting compared with other classes of drugs used to treat type 2 diabetes. The meglitinides may be used alone or in combination with metformin. Two meglitinides are approved for marketing in the United States: Prandin, derived from benzoic acid and approved by the FDA in 1997, and Starlix, derived from D-phenylalanine and approved in 2000.

1.4.6. Inhibitors of Dipeptidyl peptidase 4

Inhibitors of Dipeptidyl peptidase 4 (DPP-4) is a relatively new class of oral hypoglycemics, with two drugs, sitaglitpin and saxagliptin, having received FDA approval in 2006 and 2009, respectively. These drugs work in a way that is different from any previous diabetes treatment. They work by blocking the action of the enzyme, DPP-4, which destroys the hormone incretin; incretins help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. These hormones are released throughout the day, and levels are increased at meal times.

DPP-4 inhibitors have a major advantage over other diabetes medications in that glucose control remains stable with little or no rise in average blood glucose levels for long periods of use. With other drugs, a gradual and persistent rise in glucose levels over time is seen. This loss of drug effect has not been seen as yet with DPP-4 inhibitors or Glucagon-like Peptide-1 (GLP-1) agonists, which both work by raising GLP-1 levels in the blood. GLP-1 increases insulin levels by increasing beta cell mass and by decreasing apoptosis, or destruction of cells, especially beta cells.

1.4.7. Insulin

Insulin is produced by the beta cells in the islets of Langerhans in the pancreas. When glucose enters the blood, the pancreas should automatically produce the right amount of insulin to transport glucose into cells. Individuals with type 1 diabetes produce no insulin. Individuals with type 2 diabetes do not always produce enough insulin or they develop a resistance to the hormone that diminishes the uptake of glucose into target cells. There are currently more than 20 types of insulin products available in the United States; each form has a different time of onset and duration of action.

All currently available insulin-delivery devices require injecting insulin through the skin and into the fatty tissue below. Most individuals inject insulin with a syringe, while a smaller number of individuals use insulin pens, jet injectors, or insulin pumps. Pfizer had introduced an inhaled form of insulin onto the U.S. market in 2006, but it discontinued the inhalant October 18, 2009, because it never found acceptance among doctors and patients. Nevertheless, several other new approaches (e.g., insulin patches) for taking insulin are under development, but these remain experimental and have not yet been approved for marketing in the United States.

1.4.8. Injectable Non-Insulin Drugs – Glucagon-like Peptide-1

Non-insulin injections, such as FDA-approved exenatide (Byetta®) or liraglutide (Victoza®), are relatively new to the market, having been introduced in 2005 and 2010, respectively. Their purpose is to improve blood sugar in adults with type 2 diabetes, as well as help patients lose weight when used with a diet and exercise program. They also can be used with other medications that help control diabetes.

GLP-1 injections control blood sugar levels by mimicking incretins, the peptides that are secreted when a person eats; incretins stimulate insulin production and help individuals feel full by delaying the emptying of the stomach. GLP-1 naturally works on several deficient organs to lower blood sugar levels. It slows glucose absorption from the gut, increases insulin secretion from the pancreas when blood sugar is high, and lowers high levels of glucagon that are found in people with diabetes after meals. Its action to reduce glucagon levels causes the liver's production of excess glucose to fall and makes fasting and after-meal glucose levels easier to control.

Additionally, GLP-1 increases beta cell mass and improves first-phase insulin release. GLP-1 also attaches to an appetite receptor in the hypothalamus, which is known to decrease appetite and gradually reduce weight over time.

The multiple physiological properties of GLP-1 have made it a target for intense investigation by drug makers. Until recently, two additional GLP-1 drugs, taspoglutide and albiglutide, were undergoing clinical trials. Taspoglutide trials, however, were stopped in September 2010 because of hypersensitivity reactions and gastrointestinal side effects. While albiglutide clinical trials remain under way, it has not been determined whether it will be as effective as exanatide or liraglutide, which require two and one injections a day, respectively. Albiglutide is expected to only require one injection every four to seven days because it has a half-life of four to seven days. Four of eight trials being conducted on albiglutide will provide useful information by the end of 2010.

1.5. Side Effects of the Treatment of Diabetes

With the correct treatment and recommended lifestyle changes, individuals who have diabetes can prevent or delay the onset of complications derived from years of bodily damage caused by too much or too little blood sugar. Nevertheless, despite good self-management, treatments for diabetes have their own set of risks that patients must be aware of (Table 6). Depending on the type of medication, patients must take precautions when prescribed diabetes medications.

Table 6: Risks, Side Effects, Contraindications and Drug Interactions of Diabetes Medications, including Pre-mixed

Class	Side Effects	Precautions	Contraindications/ Critical Tests	Drug Interactions	Comments
First-generation Sulfonylureas	Hypoglycemia, weight gain, hyperinsulinemia, and disulfiram reaction with alcohol	Chlorpropamide remains active for up to 60 hours. Extreme caution is recommended for elderly patients or patients with hepatic or renal dysfunction.	Contraindicated in patients with: • Type 1 diabetes • Advanced liver disease • Advanced kidney disease sulfa allergy All drugs are metabolized in liver; periodic evaluation of liver is suggested	Anti-coagulants, salicytes, sulfonamides, androgens, chloramphenicol, ciprofloxacin clofibrate, fluconazole, fenfluramine, gemfibrozil, azole antifungals (with glyburide), methyldopa, monoamine oxidase inhibitors, probenecid, H2 antagonists, sulfinpyrazone, tricyclic antidepressants, magnesium salts and urinary acidifiers, beta blockers, calcium channel blockers, corticosteroids, thiazide diuretics, cholestyramine, hydantoins, diazoxide, estrogens, phenothiazines, sympathomimetics, rifampin,	Use of these agents is not recommended unless the patient has a well-established history of taking them. Second-generation sulfonylureas provide more predictable results with fewer side effects and more convenient dosing.

Class	Side Effects	Precautions	Contraindications/ Critical Tests	Drug Interactions	Comments
				isoniazid, nicotinic acid, urinary alkalinizers, thyroid medications and oral contraceptives, NSAIDs, naproxen, disopyramide, dicumarol, indomethacine, phenylbutazon, pentamidine angiogenesis, and converting enzymes	
Second-generation Sulfonylureas	Hypoglycemia, weight gain, and hyperinsulinemia	• Clearance may be diminished in patients with hepatic or renal impairment • Has increased potency by weight, compared with first-generation sulfonylureas • Glyburide and glipizide may increase the risk of myocardial infarction	• Advanced liver disease • Advanced kidney disease • Sulfa allergy	Anti-coagulants, salicytes, sulfonamides, androgens, chloramphenicol, ciprofloxacin clofibrate, fluconazole, fenfluramine, gemfibrozil, azole antifungals (with glyburide), methyldopa, monoamine oxidase inhibitors, probenecid, H2 antagonists, sulfinpyrazone, tricyclic antidepressants, magnesium salts and urinary acidifiers, beta blockers, calcium channel blockers, corticosteroids, thiazide diuretics, cholestyramine, hydantoins, diazoxide, estrogens, phenothiazines, sympathomimetics, rifampin, isoniazid, nicotinic acid, urinary alkalinizers, thyroid medications and oral contraceptives, NSAIDs, naproxen, disopyramide, dicumarol, indomethacine, phenylbutazon, pentamidine angiogenesis, and converting enzymes	Decreased side effects compared with first-generation drugs. Glimepiride offers best protection against coronary artery disease. Glipizide is preferred with renal impairment. Doses >15 mg should be divided. Glimepiride indicated for use with insulin. Shown to have some insulin-sensitizing effect.
Meglitinides	Hypoglycemia, weight gain, and hyperinsulinemia	Use with caution on patient with hepatic or renal impairment	• Advanced liver disease • Advanced kidney disease • Hypersensitivity reaction to Sulfa	Interacts with gemfibrozil (Lopid; a cholesterol-lowering medicine) and the combination of gemfibrozil and itraconazole (the antifungal Sporanox), which raise the blood levels of repaglinide roughly 28-fold and 72-fold, respectively. Other drugs include: barbiturates, corticosteroids, thiazide diuretics, carbamazapine, rifampin, calcium channel blockers, NSAIDS, monoamine oxidase inhibitors, sulfonamides, erythromycin, non-selective beta blockers, probenecid, isoniazid, nicotinic acid, estrogens, phenytoin, sympathomimetics,	Patients should be instructed to take medication no more than 30 minutes prior to a meal. If meals are skipped or added, the medication should be skipped or added as well. Approved for use as monotherapy or in combination with TZD or metformin.

Class	Side Effects	Precautions	Contraindications/ Critical Tests	Drug Interactions	Comments
				phenothiazines, thyroid supplements and some oral contraceptives.	
Phenylalanine derivative (meglitinides)	Minimal risk of hypoglycemia	Currently no contraindications available. Use with caution with moderate to severe hepatic disease.	• Advanced liver disease Periodic evaluation of liver function	Interacts with gemfibrozil (Lopid, a cholesterol-lowering medicine) and the combination of gemfibrozil and itraconazole (the antifungal Sporanox), which raise the blood levels of repaglinide roughly 28-fold and 72-fold, respectively. Other drugs include: barbiturates, corticosteroids, thiazide diuretics, carbamazapine, rifampin, calcium channel blockers, NSAIDS, monoamine oxidase inhibitors, sulfonamides, erythromycin, non-selective beta blockers, probenecid, isoniazid, nicotinic acid, estrogens, phenytoin, sympathomimetics, phenothiazines, thyroid supplements and some oral contraceptives. Note: Drug interactions are less likely with nateglinide than repaglinide (above), but medicine should be used with caution.	Approved as monotherapy or in combination with metformin or TZD. Has only 2-hour duration of action. If meals are skipped or added, the medication should be skipped or added as well. Less likely to cause weight gain than repaglinide.
Biguanide	Nausea, diarrhea, metallic taste, and possible lactic acidosis	Due to increased risk of lactic acidosis, should not use if suspect frequent alcohol use, liver or kidney disease, or congestive heart failure (CHF)	Contraindicated if serum creatinine is: >1.5 mg/dL in men or >1.4 mg/dL women. Do not use if creatinine clearance is abnormal. Monitor hematological and renal function annually.	Calcium channel blockers; antibiotics trimethoprim or vancomycin; diuretics including amiloride and furosemide; gastrointestinal medications cimetidine or ranitidine; heart medication digoxin, especially if used alongside metformin; morphine, the anti-malaria drug quinine; blood thinner warfarin; alcohol; and herb ginkgo biloba and others	Especially beneficial in obese patients due to potential for weight loss, improved lipid profile, and lack of potential for hypoglycemia requiring supplemental carbohydrate intake. Discontinue for 48 hours after contrast dye procedures.
Thiazolidinedione (rosiglitazone)	Minor weight increase of 3–6 lbs., edema	Should not be used in patients with CHF or hepatic disease. Can cause mild-to-moderate edema.	Should be avoided if Alanine transaminase (ALT) >2.5X upper limit of normal. Measure ALT periodically. Discontinue if ALT >3X upper limit of normal.	Blood pressure medication Bosentan, beta-blockers, azole anti-fungals, chloramphenicol, clofibrate, fenfluramine, metformin, monoamine oxidase inhibitors, non-steroidal anti-inflammatory drugs, phenylbutazone, probenecid, quinolone antibiotics,	Approved for use as monotherapy and in combination with metformin, sulfonylureas, or insulin. Fewer interactions associated with CYP-450.

Class	Side Effects	Precautions	Contraindications/ Critical Tests	Drug Interactions	Comments
				salicylates such as aspirin plus sulfonamides, anticoagulants including warfarin, and alcohol.	
Thiazolidinedione (pioglitazone)	Minor weight increase of 3–6 lbs., edema	Should not be used in patients with CHF or hepatic disease. Can cause mild to moderate edema.	Should be avoided if ALT >2.5X upper limit of normal. Measure ALT periodically. Discontinue if ALT >3X upper limit of normal.	Blood pressure medication Bosentan, beta-blockers, azole anti-fungals, chloramphenicol, clofibrate, fenfluramine, metformin, monoamine oxidase inhibitors, non-steroidal anti-inflammatory drugs, phenylbutazone, probenecid, quinolone antibiotics, salicylates such as aspirin, plus sulfonamides, anticoagulants including warfarin, and alcohol	
Alpha-glucosidase inhibitor	Hypoglycemia possible if used with insulin; gas and bloating, sometimes diarrhea for both drugs	Should not be used if GI disorders are concurrent	Should be avoided if serum creatinine is >2.0 mg/dL. Monitor serum transaminase every 3 months for first year of therapy. Contraindicated in GI conditions.	Somatropin may decrease the efficacy of oral antidiabetic agents such as acarbose and miglitol	Approved for use as monotherapy and in combination with metformin, sulfonylureas, or insulin. If used with hypoglycemic agents, such as sulfonylureas or insulin, must treat hypoglycemia with glucose not sucrose.
Inhibitors of Dipeptidyl peptidase 4 (DPP-4)	Stuffed or runny nose, sore throat, headache, diarrhea, stomach pain, flatulence, nausea, metallic taste	Precautions are stipulated for people who have allergies, kidney problems, are pregnant or are/will breastfeed. New FDA alert shows a link between sitagliptin and pancreatitis.	Contraindicated for people with: type 1 diabetes and moderate renal insufficiency	Dosage should be reduced when co-administered with potent CYP 3A4 inhibitors	DPP-4 pharmacodynamic properties do not have a high risk of drug interactions; however, because these drugs are relatively new, clinical trials are under way.
Pre-mixed Insulins					
Glucovance® (glyburide and metformin)	Hypoglycemia, weight gain, lactic acidosis	Should not be used if suspect frequent alcohol use, liver or kidney disease, or CHE	Same caveats as individual components	Same caveats as individual components	Patients may frequently use 2 different dose tablets to attain desired daily dosage and results. Discontinue for 48 hours after procedure using contrast dye. Hypoglycemia, weight gain.

Class	Side Effects	Precautions	Contraindications/ Critical Tests	Drug Interactions	Comments
Metaglip® (glipizide and metformin)	Hypoglycemia, weight gain, lactic acidosis	Should not be used if suspect frequent alcohol use, liver or kidney disease, or CHE	Same caveats as individual components	Same caveats as individual components	Patients may frequently use 2 different dose tablets to attain desired daily dosage and results. Discontinue for 48 hours after procedure using contrast dye. Edema, possible lactic acidosis.
Avandamet® (rosiglitazone and metformin)	Edema, possible lactic acidosis	Should not be used if suspect frequent alcohol use, liver or kidney disease, or CHE	Same caveats as individual components	Same caveats as individual components	Less expensive than using agents separately. Reported decrease in GI upset associated with metformin and weight increase associated with rosiglitazone. Discontinue for 48 hours after procedure using contrast dye.
Actoplus Met® (pioglitazone and metformin)	Same caveats as individual components	Same caveats as individual components	Same caveats as individual components	Same caveats as individual components	
Avandaryl® (rosiglitazone and glimepiride)	Same caveats as individual components	Same caveats as individual components	Same caveats as individual components	Same caveats as individual components	

1.6. Diabetes and Driver Safety

A number of acute and chronic complications associated with diabetes may affect driving competency. Chronic complications associated with diabetes mellitus that may compromise driver safety include, but are not limited to, cardiovascular disease, diabetic neuropathy, and diabetic retinopathy. The effects of the chronic complications of diabetes mellitus on driving ability are beyond the scope of this report. However, a brief description of these complications is provided at the end of this section.

The most important acute threat to driver safety among individuals with diabetes mellitus is generally considered to be hypoglycemia. Hypoglycemia is a clinical syndrome that results from abnormally low levels of blood glucose, which can arise as a result of treatments for diabetes. The symptoms of hypoglycemia can vary from person to person, as can their severity. In general, however, the body's biochemical response to hypoglycemia usually starts when blood sugar levels fall below 65 to 70 mg/dl (3.6 to 3.9 mmol/L). Below this point, the body responds by increasing the secretion of counter-regulatory hormones. If the blood glucose level falls below 60 mg/dl (3.3 mmol/L), physical symptoms begin to become apparent – the onset of sweating, tremor, hunger, a feeling of anxiety, and palpitations. These symptoms, when recognized, act as a warning signal to individuals with diabetes that they should take

immediate steps to increase their blood glucose levels. If these warning signs are ignored (or go unrecognized – hypoglycemic unawareness) blood glucose levels may continue to fall. When blood glucose levels fall below 50 mg/dl (2.8 mmol/L), the central nervous system begins to be starved of glucose and symptoms of neuroglycopenia (weakness, lethargy, blurred vision, dizziness, trouble speaking) and cognitive dysfunction begin to occur. Further reductions in blood glucose levels may result in seizures, coma, and death.

1.6.1. The Occurrence of Hypoglycemia While Driving

A number of studies have attempted to determine the proportion of individuals with diabetes who have experienced a hypoglycemic event while driving. The findings from a sample of these studies are summarized in Table 7. These data show that experiencing a hypoglycemic episode while driving is not a rare event and that a significant proportion of individuals attribute a crash that they were involved in to hypoglycemia.

Table 7: Occurrence of Hypoglycemia While Driving

Reference	Year	N=	Diabetes Type (Special Population)	Percent of Drivers **Experiencing ≥1** Hypoglycemic Episode while Driving	Percent of Drivers Experiencing **≥1** Crash Attributed to Hypoglycemia
Cox et al.[14]	2009	452	Type 1	• Disruptive moderate hypoglycemia that impaired driving was the most common event • 52% reported at least 1 hypoglycemia-related driving mishap over the 1-year time frame examined prospectively • 32% reported 2 or more hypoglycemia-related driving mishap over the 1 year time frame	2.4% reported a collision attributed to hypoglycemia over the 1-year time frame examined prospectively
Cox et al.[15]	2003	673	Type 1 (n=341)	• 22% in previous 6 months • 17% experienced a severe hypoglycemic event while driving in previous 2 years	NR
			Type 2 (n=332)	• 4% in previous 6 months • 5% experienced a severe hypoglycemic event while driving in previous 2 years	NR
MacLeod et al.[16]	1993	600	Type 1 (n=544) Type 2* (n=54)	NR	2.9% in previous year
Ward et al.[17]	1990	158	Type 1 diabetes	40% during driving life	13% during driving life
Stevens et al.[18]	1989	354	Type 1 diabetes	18.4% in previous year	12% during driving life
Eadington et al.[19]	1989	187	Type 1 diabetes	NR	3.7% during previous 8 years
Songer et al.[20]	1988	127	Insulin dependent	NR	5.2% during driving life
Clarke et al.[21]	1980	157	Type 1 diabetes	40.4% during driving life	NR
Frier et al.[22]	1980	250	Insulin dependent	34.4% over driving life	5.0% during driving life

* All individuals with type 2 diabetes insulin-treated

1.6.3. Hypoglycemic Unawareness

Hypoglycemic unawareness is the reduced ability or failure to recognize hypoglycemia at the physiological plasma glucose concentration at which warning symptoms normally occur. Patients with hypoglycemia unawareness either do not realize that the plasma glucose is decreasing, or they ultimately feel the symptoms, but at much lower plasma glucose levels than normal. Such individuals are more prone to incapacitation consequent to hypoglycemia because preventative action that will increase blood glucose levels is not taken in a timely manner. In an individual with normal hypoglycemic awareness, the first response to a drop in plasma glucose level below 70 to 65 mg/dl is the acute release of counter-regulatory hormones (glucagon and epinephrine). In some individuals with type 1 diabetes, the protective glucagon response to hypoglycemia begins to fail within two years of the onset of the disease. The prevalence of hypoglycemia unawareness becomes more common among individuals with type 1 diabetes as the duration of the disease increases. The etiology underlying the development of hypoglycemic unawareness is not known.

Hypoglycemia unawareness is of particular concern in a discussion of driver safety. Decisions to drive during hypoglycemia are variable across studies and appear to be related to an individual's ability to recognize the onset of hypoglycemia. In a 2000 study by Cox et al.[23], only 22 percent of type 1 diabetes subjects pulled over or undertook corrective action while performing a driving simulator task during induced hypoglycemia. In another study of type 1 diabetes patients with induced hypoglycemia (2.8 mmol/L), 22 percent to38 percent of the patients judged that they could drive safely[24]. Cox et al.[25] suggest that taking corrective action during hypoglycemia is associated with normal awareness of hypoglycemia. In a 2007 study by Stork et al.[26], decisions about whether or not to drive during hypoglycemia were examined. Table 8 below provides a summary of this study.

Table 8: Stork et al. 2007 Study Characteristics

Reference	Year	N	Study Groups	Surveyed in Two States
Stork et al. [28]	2007	24	Type 1 normal awareness (T1Norm)	• Euglycemia (5.0 mmol/L) • Induced hypoglycemia (2.7 mmol/L) Asked if they felt hypoglycemic, and if they would drive.
		21	Type 1 impaired awareness (T1Imp)	
		22	Type 2 (T2)	

During the euglycemic testing condition, when individuals were queried about their glycemic status, and whether or not they would drive, the following results were observed.

T1Norm group

When asked whether they felt hypoglycemic, 22 patients in the T1Norm group (91.7 percent) stated that they did not feel hypoglycemic and two (8.3 percent) answered "maybe." Yet, in response to the question whether they would currently drive in everyday life, seven (29.2 percent) declared that they would first measure their blood glucose before driving. Only one subject answered "maybe" to the latter question (4.5 percent).

T1Imp Group

Four patients answered "maybe" to the question about feeling hypoglycemic (19 percent), and eight (38.1 percent) would first measure their blood glucose before driving, whereas one subject (4.8 percent) would "maybe" drive.

T2 Group

One patient answered that he was "maybe" hypoglycemic (5 percent), and all others answered "no" (95 percent). Two patients in this group stated that they would first measure their blood glucose (10 percent), and three (15 percent) said that they would not drive in their current condition.

Analysis of the Decision to Drive

During euglycemia, the decision not to drive (or to measure blood glucose before driving) was not made more frequently by patients in the T1Norm than in the T1Imp group ($\chi 2 = 0.11$; $P = 0.74$) or by patients in the T2 group ($\chi 2 = 0.36$; $P = 0.55$). This was no different for patients using insulin ($\chi 2 = 0.26$; $P = 0.61$) or for patients using oral hypoglycemic agents ($\chi 2 = 0.19$; $P = 0.66$).

The results of these same individuals when tested under the hypoglycemic condition are reported in Table 9, below.

Table 9: Stork et al. 2007 Study Results During Hypoglycemia (2.7 mmol/L)

Do you feel hypoglycemic?	*n* (%)	Would you currently drive?	*n* (%)
T1Normal Awareness group (*n* = 24)			
Yes	15 (62.5)	Drive	0 (0)
		Maybe	1 (7)
		Measure glucose	3 (20)
		Not drive	11 (73)
Maybe	9 (37.5)	Drive	0 (0)
		Maybe	0 (0)
		Measure glucose	8 (89)
		Not drive	1 (11)
No	0 (0.0)	Drive	NA
		Maybe	NA
		Measure glucose	NA
		Not drive	NA
T1Impaired awareness group (*n* = 21)			
Yes	0 (0.0)	Drive	NA
		Maybe	NA
		Measure glucose	NA
		Not drive	NA
Maybe	8 (38.1)	Drive	0 (0)
		Maybe	0 (0)
		Measure glucose	5 (63)
		Not drive	3 (38)
No	13 (61.9)	Drive	9 (69)
		Maybe	0 (0)
		Measure glucose	3 (23)
		Not drive	1 (8)
T2 group (n = 20)			
Yes	11 (55.0)	Drive	0 (0)
		Maybe	0 (0)
		Measure glucose	5 (45)
		Not drive	6 (55)
Maybe	9 (45.0)	Drive	3 (33)
		Maybe	2 (22)

Do you feel hypoglycemic?	*n* (%)	Would you currently drive?	*n* (%)
		Measure glucose	2 (22)
		Not drive	2 (22)
No	0 (0.0)	Drive	NA
		Maybe	NA
		Measure glucose	NA
		Not drive	NA

Stork et al. commented that many of the individuals with type 1 diabetes with impaired hypoglycemia awareness (43 percent) failed to decide not to drive during experimental hypoglycemia. The authors noted that this was not surprising given that these patients were not conscious of their hypoglycemic condition. Conversely, only 1 of 24 patients (4.2 percent) with type 1 diabetes and normal hypoglycemia awareness chose to drive while (symptomatically) hypoglycemic. The more striking finding from this study was that a relatively large proportion of individuals with type 2 diabetes (~25 percent) with normal awareness indicated that they would drive while positive or in doubt whether they were hypoglycemic. These results suggest that educating patients with diabetes about driver safety issues is critical.

1.7. Complications of Diabetes

Individuals with diabetes are at high risk for a number of complications. Because the disease is a lifelong one, over time, high levels of sugar in the blood can lead to serious problems throughout the body, damaging the heart, eyes, kidneys, nerves, and other organs. Additionally, complications from diabetes affect different segments of the population disproportionately (Table 10).

1.7.1. Heart Disease and Stroke

Adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes, and the risk for stroke is two to four times higher (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2008). High blood sugar damages blood vessels and can lead to blockage. In the heart, this blockage can cause heart attacks. In the brain, it can cause stroke. Depending on the area in the brain affected by these circulatory problems, memory can be affected as well.

Even when glucose levels are under control, diabetes increases the risk of heart disease and stroke, but the risks are even greater if blood sugar is not well controlled, according to the American Heart Association (AHA). About 75 percent of people with diabetes die from some form of heart or blood vessel disease (AHA, 2010).

1.7.2. High Blood Pressure

As many as two out of three adults with diabetes have high blood pressure (ADA, 2010). Diabetes adversely affects the arteries, predisposing them to atherosclerosis (hardening of the arteries). If not treated, high blood pressure can lead to blood vessel damage, stroke, heart failure, heart attack, or kidney failure.

1.7.3. Blindness

Diabetes is the leading cause of new cases of blindness among adults ages 20 to 74 years (NIDDK, 2008). Diabetic retinopathy – damage to blood vessels of the light-sensitive tissue at the back of the eye – causes 12,000 to 24,000 new cases of blindness each year.

Diabetic retinopathy can develop in anyone who has type 1 or type 2 diabetes. The longer an individual has diabetes, and the less controlled his or her blood sugar is, the more likely the individual is to develop diabetic retinopathy. At first, diabetic retinopathy may cause no symptoms or only mild vision problems. Eventually, however, diabetic retinopathy can result in blindness.

1.7.4. Kidney Disease

Diabetes is the leading cause of new cause of kidney failure, accounting for 44 percent of new cases in 2005 (United States Renal Data System [USRDS], 2007). High blood pressure is a major factor in the development of kidney problems, as well as damage to the kidneys from diabetes.

Diabetic kidney disease takes many years to develop, and rarely does it develop in the first 10 years of diabetes (NKUDIC [National Kidney and Urologic Diseases Information Clearinghouse], 2008). Typically, 15 to 25 years will pass before kidney failure occurs. For people who live with diabetes for more than 25 years without any signs of kidney failure, the risk for ever developing it decreases.

1.7.5. Nervous System Disease

About 60 to 70 percent of people with diabetes have mild to severe forms of nervous system damage, caused by high blood sugar levels and low blood sugar levels (NIDDK, 2008). Research has shown that people who kept their blood glucose as close to normal were able to lower their risk of nerve damage (NIDDK, 2008).

The results of nerve damage to the peripheral nerves – caused by high levels of blood sugar – include impaired sensation or pain in the feet or hands, carpal tunnel syndrome, and weakness of the arms and legs. Almost 30 percent of people ages 40 years or older with diabetes have impaired sensation in the feet – for example, at least one area that lacks feeling (NIDDK, 2008). Severe forms of diabetic nerve disease are a major contributing cause of lower-extremity amputations.

Nerve damage to the autonomic nerves – caused by too many instances of low blood sugar – makes it difficult for people to feel symptoms of hypoglycemia, and can cause slowed digestion, erectile dysfunction, increased or different rates of heart speed, urinary difficulties and bladder infections, and sudden changes in blood pressure, among other problems.

1.7.6. Amputations

More than 60 percent of nontraumatic lower-limb amputations occur in people with diabetes. Diabetes can impair blood flow and cause nerve damage to the feet (NIDDK, 2008). When the feet's network of nerves is damaged, the sensation of pain is reduced, causing people to not realize they've injured themselves. Left untreated, a minor foot injury could become a serious infection, especially with reduced blood flow; wounds do not heal as well. Severe damage might require toe, foot or even leg amputation.

1.7.7. Other Complications

- Uncontrolled diabetes often leads to biochemical imbalances that can cause acute life-threatening events, such as diabetic ketoacidosis and hyperosmolar, or nonketotic, coma.

- People with diabetes are more susceptible to many other illnesses and, once they acquire these illnesses, often have worse prognoses. For example, they are more likely to die with pneumonia or influenza than people who do not have diabetes.
- People ages 60 years or older with diabetes are two to three times more likely to report an inability to walk a quarter of a mile, climb stairs, do housework, or use a mobility aid compared with people without diabetes in the same age group.

Table 10: Segments of the Population Disproportionally Affected by Diabetes and Complications of Diabetes

Population Group	Key Notes
Men	• 12 million, or 11.2 percent, of all men ages 20 years or older have diabetes
Women	• Women with diabetes are also more likely to have a heart attack, and at a younger age, than women without diabetes • The prevalence of diabetes is at least 2 to 4 times higher among women who are African American, Hispanic/Latino, American Indian, and Asian/Pacific Islander • The risk for diabetes also increases with age for women. Because of the increasing lifespan of women and the rapid growth of minority populations, the number of women in the United States at high risk for diabetes and its complications is increasing • Women who have had gestational diabetes or have given birth to a baby weighing more than 9 pounds are at an increased risk for developing type 2 diabetes later in life
Pregnant women	• For women who do not currently have diabetes, pregnancy brings the risk of gestational diabetes • Gestational diabetes develops in 2 to 5 percent of all pregnancies but disappears when a pregnancy is over
Seniors	• 12.2 million, or 23.1 percent, of all people age 60 and older have diabetes • Feet complications are among the most prevalent • Neuropathy is common
African Americans	• African Americans are 1.8 times more likely to have diabetes than are non-Hispanic whites • 3.7 million, or 14.7 percent, of all African Americans aged 20 years or older have diabetes • 25 percent of African Americans between the ages of 65 and 74 have diabetes • 1 in 4 African-American women over 55 years of age has diabetes • African Americans are almost 50 percent as likely to develop diabetic retinopathy as non-Hispanic whites • African Americans are 2.6 to 5.6 times as likely to suffer from kidney disease, with more than 4,000 new cases of end stage renal disease (ESRD) each year • African Americans are 2.7 times as likely to suffer from lower-limb amputations. Amputation rates are 1.4 to 2.7 times higher in men than women with diabetes
Hispanic/Latinos	• Among non-Hispanic white youths ages 10 to 19 years, the rate of new cases of type 1 diabetes was higher than for type 2 diabetes
Native Americans	• American Indians and Alaska Natives have a 2.2 times higher likelihood of developing diabetes compared with non-Hispanic whites • Between 1994 and 2004, the percentage of American Indian and Alaska Native youth aged 15-19 years to be diagnosed with diabetes increased 68 percent • 95 percent of American Indians and Alaska Natives who are diabetic have type 2 diabetes • An estimated 30 percent of American Indians and Alaska Natives have pre-diabetes
Asian Americans, Native Hawaiians & Other Pacific Islanders	• 7.5 percent of Asian Americans aged 20 and older have diabetes • For youths ages 10 to 19 years, the rate of new cases of type 2 is greater than the rate of type 1 diabetes

Source: NIDDK, 2008

Section 2: Federal Regulatory and Medical Advisory Criteria for CMV Operators

2.1. Current Federal Regulatory Criteria for CMV Operators

Federal Motor Carrier Safety Regulations (FMCSRs), found in 49 Code of Federal Regulations (CFR) 301 through 399, cover businesses that operate CMVs in interstate commerce. FMCSRs that pertain to fitness to drive a commercial vehicle are found in 49 CFR 391 Subpart E. Only motor carriers engaged purely in intrastate commerce are not directly subject to these regulations. However, intrastate motor carriers are subject to state regulations, which must be identical to, or compatible with, the federal regulations in order for states to receive motor carrier safety grants from the Federal Motor Carrier Administration (FMCSA). States have the option of exempting CMVs with a gross vehicle weight rating of less than 26,001 lbs.

The following subsection contains the federal regulatory and medical advisory standards found in the FMCSRs (49 C.F.R. section 391.41) that specifically apply to drivers with diabetes mellitus. Complete FMCSRs can be found at the Web site: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrguide.asp?section_type=A.

Country	United States
STANDARD	§ 391.41 Physical qualifications for drivers. (b)(8) A person is physically qualified to drive a commercial motor vehicle if that person: (b)(3) Has no established medical history or clinical diagnosis of diabetes mellitus currently requiring insulin for control
Medical advisory criteria	Diabetes mellitus is a disease which, on occasion, can result in a loss of consciousness or disorientation in time and space. Individuals who require insulin for control have conditions that can get out of control by the use of too much or too little insulin, or food intake not consistent with the insulin dosage. Incapacitation may occur from symptoms of hyperglycemic or hypoglycemic reactions (drowsiness, semi-consciousness, diabetic coma, or insulin shock). The administration of insulin is, within itself, a complicated process requiring insulin, syringe, needle, alcohol sponge and a sterile technique. Factors related to long-haul commercial motor vehicle operations such as fatigue, lack of sleep, poor diet, emotional conditions, stress, and concomitant illness compound the diabetic problem. Because of these inherent dangers, the FMCSA has consistently held that a diabetic who uses insulin for control does not meet the minimum physical requirements of the FMCSR. Hypoglycemic drugs, taken orally, are sometimes prescribed for diabetic individuals to help stimulate natural body production of insulin. If the condition can be controlled by the use of oral medication and diet, then an individual may be qualified under the present rule. See Conference Report on Diabetic Disorders and Commercial Drivers and Insulin-Using Commercial Motor Vehicle Drivers at: http://www.fmcsa.dot.gov/rulesregs/medreports.htm Diabetes Exemption Program criteria available at: http://www.fmcsa.dot.gov/documents/safetyprograms/Diabetes/diabetes-exemption-package0706.pdf

Below, we have provided a comparison of the recommendations and standards available in a number of countries regarding diabetes and fitness to drive. Regulations and guidelines from the following nations are included:

- **United States** (Part 391.41: Physical qualifications for drivers, FMCSA; 2010);
- **Australia** (Assessing Fitness to Drive; Medical Standards for Licensing and Clinical Management Guidelines; 2006)**;**

- **Canada** (Canadian Council of Motor Transport Administrators [CCMTA] Medical Standards for Drivers; 2008)**;**
- **New Zealand** (Medical Aspects of Fitness to Drive. A Guide for Medical Practitioners; Land Transport Safety Authority; 2009)**;**
- **Sweden** (Swedish National Road Administration provisions on the medical requirements for possession of a driving license, etc.; 1998);
- **United Kingdom** (For Medical Practitioners: At A Glance Guide to the Current Medical Standards of Fitness to Drive, Issued by Drivers Medical Group, Driver and Vehicle Licensing Agency of the Department for Transport [DVLA], Swansea; 2010).
- **Mexico** (Physical and Medical Qualifications Standards for Mexico-domiciled Federal-licensed Vehicle Drivers; 2009).

Table 11 below provides a quick-view assessment of the similarities between the regulations and guidance of other countries compared with the United States. Appendix F provides the detailed recommendations and standards for other countries regarding diabetes and CMV fitness to drive.

Table 11: Quick-view of the Most Relevant Standards by Different Countries

	U.S.	Australia	Canada	New Zealand	Sweden	United Kingdom	Mexico
Diabetes controlled by insulin	Cannot drive	Cannot drive unless certain conditions are met	Cannot drive unless certain conditions are met	Cannot drive unless certain conditions are met	Cannot drive unless certain conditions are met	Cannot drive unless a driver was licensed before January 4, 1991, and on insulin	Cannot drive
Conditional license allowed	Yes Exemption program	Yes	Yes	Yes	Yes	Yes Individuals are dealt with individually and subject to annual assessment	No
Conditions /criteria for a conditional license		• Condition well-controlled • Absence of hypoglycemic episodes • Awareness of sensation of hypoglycemia • Taking agents to provide minimal risk of hypoglycemia • Absence of end organ effects, which may affect driving	• No episode of hypoglycemia within two years • No evidence of hypoglycemia unawareness • Condition well-controlled: Glyosylated hemoglobin is <2.0 times the upper limit of normal; and less than 10% of blood glucose levels are <4 mmol/L • Log maintained • Knowledge of disease • No other disqualifying complications • Observes guidelines dated 1991 • Annual medical review and examination by ophthalmologist	• Nocturnal insulin therapy treatment provided • Treatment regiment considered satisfactory • Adequate glycemic control • No complications of diabetes • Must pass a medical exam every six months that shows: o adherence to treatment o proof of self-blood testing of blood glucose with satisfactory levels o absence of hypoglycemic episodes or unawareness o the absence of significant diabetic complications • Regular pattern of shifts with meal breaks	• Diabetes mellitus requiring insulin treatment constitutes grounds for denial of possession in Groups II and III. However, if the disease is well-balanced, possession in category C may be granted. In such cases, possession shall be limited such that a heavy lorry may not be driven in traffic that is classified as commercial in the provisions of the Commercial Traffic Act (1998:490) • In the case of diabetes mellitus treated with insulin, a reappraisal shall be made after one year and thereafter at least every third year	Drivers may apply or renew licenses for small lorries with or without a trailer if they meet the following conditions: • Had no hypoglycemic attacks requiring assistance while driving within the previous 12 months • Condition has been stable for a period of at least one month • Check blood glucose levels at least twice daily and at times relevant to driving (advises use of memory chip meter) • Must be examined by a diabetes specialist and provide blood glucose records for the last 3 months • Does not have any other condition that would render them a danger • Sign an undertaking to comply with doctors' directions and report any significant changes	

Australia, Canada, New Zealand, Sweden and the United Kingdom all offer conditional licenses for such individuals, but their standards vary. The United Kingdom and Sweden are the only two that don't allow insulin users to drive certain CMVs; the UK and Sweden do not allow certification for use of heavy lorries, and Sweden also excludes people from driving buses and trailers.

Nearly all of the countries assessed – excluding the U.S and Mexico – stipulate the disease must be well-controlled, they require there be an absence of hypoglycemic episodes. Canada and the UK, however, are the only two that define a period of time in which a driver must not have experienced such incidents. Canada requires two years, and the UK stipulates one year.

Australia and Canada are the only two countries that require that drivers have no evidence of hypoglycemia unawareness, and Australia is the only country to require that a driver take agents to provide minimal risk of hypoglycemia.

Canada is the only country to define what "control" means: Hemoglobin is < 2.0 times the upper limit of normal; and less than 10 percent of blood glucose levels are < 4 mmol/L. While Canada and New Zealand stipulate that a log or proof must be maintained, the UK is more stringent, requiring that blood glucose levels be checked at least twice daily, preferably using a memory chip meter.

All countries that offer a conditional license, excluding Sweden, require that individuals be free of complications from diabetes, such as having additional medical conditions that would impair driving. And all countries require drivers to receive a higher standard of medical assessment and to have medical assessments more frequently than healthy drivers.

A comparison of the regulatory standards and guidelines from the United States to other national regulations and guidelines for CMV drivers is provided in Appendix F. A brief history of the CMV driver regulations concerning diabetes policy is provided in Appendix G.

2.2. Current State Regulatory Criteria for CMV Drivers

As stated at the beginning of the *Current Federal Regulatory and Medical Advisory Criteria for CMV Operators* section, motor carriers engaged purely in intrastate commerce are not directly subject to FMCSRs, found in 49 CFR 301 through 399 regulations. State regulations for intrastate motor carriers must be identical to, or compatible with, the federal regulations in order for states to receive motor carrier safety grants from FMCSA.

There are wide disparities in intrastate medical waiver programs across the United States. Overall, 27 states will consider issuing a waiver for IDDM if the CMV driver has a good safety record and agrees to added restrictions and monitoring. In 25 states there are no waivers for CMV drivers with insulin-treated diabetes. Table 12 below lists diabetic waivers for CMV drivers with insulin-treated diabetes by state as of January 2011. State-specific rules are presented in Appendix H.

Table 12: Diabetic Waivers by State

State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA
Alabama	No	Kentucky	Yes	North Dakota	No
Alaska	NA	Louisiana	No	Ohio	No
Arizona	No	Maine	No	Oregon	Yes
Arkansas	No	Maryland	No	Pennsylvania	Yes

State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA	State	Waiver – Yes, No, NA
California	Yes	Massachusetts	Yes	Rhode Island	Yes
Colorado	Yes	Michigan	Yes	South Carolina	No
Connecticut	Yes	Minnesota	Yes	South Dakota	No
D.C.	No	Mississippi	No	Tennessee	Yes
Delaware	Yes	Missouri	No	Texas	No
Florida	Yes	Montana	Yes	Utah	Yes
Georgia	No	Nebraska	No	Vermont	Yes
Hawaii	No	Nevada	Yes	Virginia	Yes
Idaho	No	New Hampshire	Yes	Washington	Yes
Illinois	No	New Jersey	No	West Virginia	Yes
Indiana	No	New Mexico	Yes	Wisconsin	Yes
Iowa	No	New York	Yes	Wyoming	Yes
Kansas	Yes	North Carolina	Yes		

Section 3: Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for the report. The section briefly covers the key questions addressed, literature searches performed, the criteria used, including studies, evaluation of study quality, 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, statistical approaches used, etc., are documented in appendices.

3.1. Key Questions

This evidence report addresses four key questions. Each of these key questions was developed by the FMCSA such that the answers to these questions provided information that would be useful in updating their current physical qualification standards and guidance to medical examiners. The four key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with diabetes mellitus?

In addressing this question we examine the relationship between hypoglycemia and the following direct and indirect outcome measures:

a. Simulated driving performance (indirect)
b. Driving-related cognitive and psychomotor performance (indirect)

Key Question 3: What risk factors are associated with an increased incidence of severe hypoglycemia, and what is the incidence of severe hypoglycemia with different treatments and treatment modalities (e.g., use of injectable, non-insulin drugs such as Byetta®)?

Potential factors to be assessed in addressing this question include the following:

a. Mechanism of glycemic control (insulin, first generation sulfonylureas, second generation sulfonylureas, meglitinides, and other hypoglycemic drugs used to control blood glucose levels)
b. Route of insulin administration (inhaled, subcutaneous injection, pump)

Key Question 4: How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

3.2. Identification of Evidence Bases

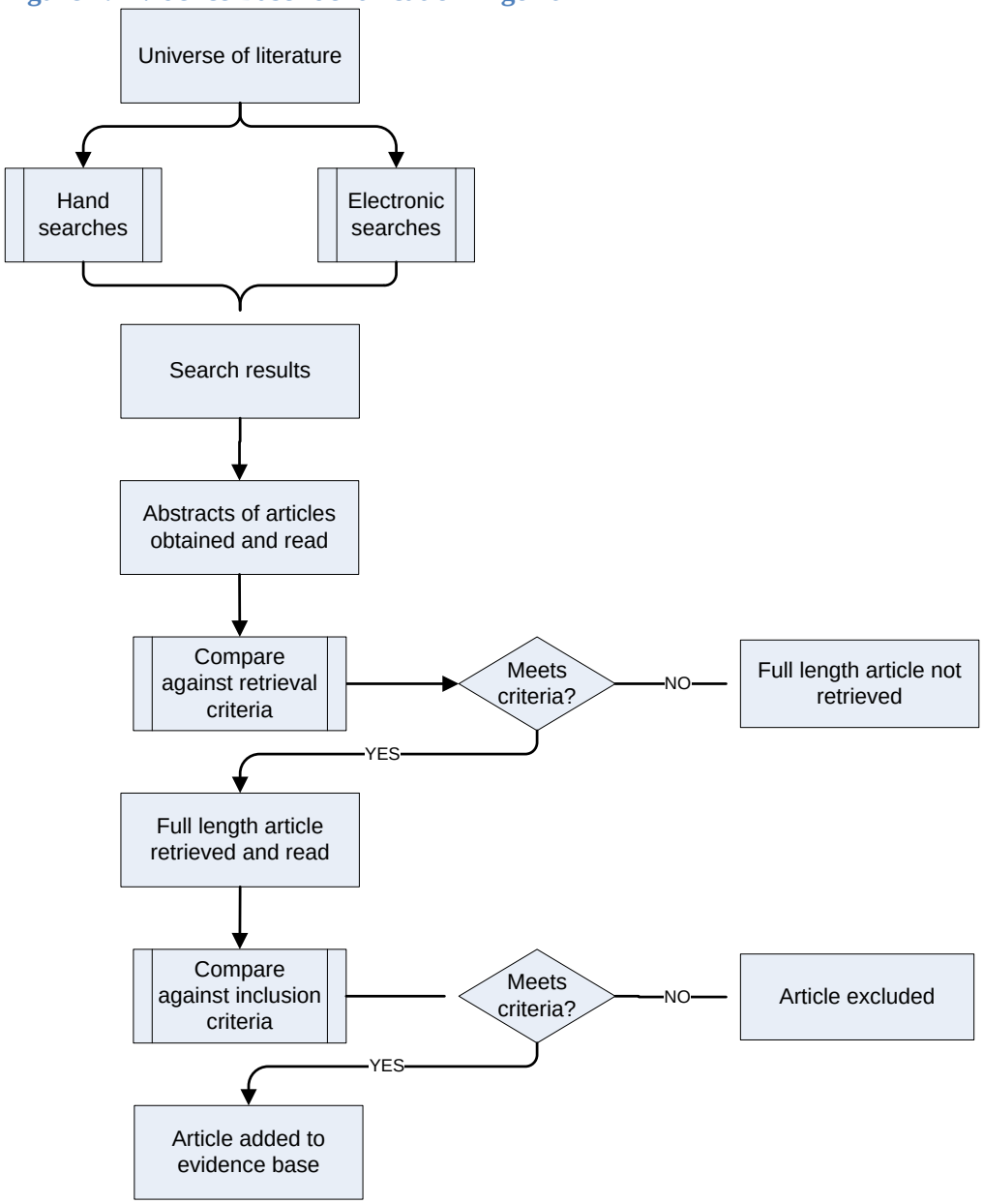
This section of the report is largely reproduced from the 2006 version of this report. Information about how the searches were updated for the current revision is also provided.

The individual evidence bases for each of the key questions 1, 2, and 4 addressed in this evidence report were identified using the multistaged process captured by the algorithm presented in Figure 2. Note that while searches of electronic databases were conducted for Key Question 3, retrieval and inclusion criteria were not applied in the same manner as for Key Questions 1, 2, and 4. The primary reason is that this

section was meant only to address what is known in the literature about risk factors for severe hypoglycemia and how treatment-related factors impact the incidence of hypoglycemia. The literature available for this topic is extensive, and a systematic summary of this literature is beyond the scope and need of this report. Instead, we examined available systematic reviews and meta-analyses that addressed this question, and summarize the findings relevant to Key Question 3 using figures and tables.

The first stage of our literature review process consists of a comprehensive search of the literature. Searches for the 2006 report were conducted by ECRI Institute. In the review, literature searches were conducted by MANILA Consulting. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles are to 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 2: Evidence Base Identification Algorithm



3.2.1. 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, which use a less rigorous approach to identifying and obtaining literature, thereby allowing 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 original search strategies, and those used to update this report, are presented in Appendix A.

3.2.1.1. Electronic Searches

For the 2006 version of this report, we performed comprehensive searches of the electronic databases for the period of 1966 through May 19, 2006. The databases searched are listed in Table 13.

Table 13: Electronic Databases Searched in the 2006 Report

Name of database	Date limits
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 - April 10, 2006
Cochrane Library	Through 2006 Issue 2
Embase (Excerpta Medica)	1980 - April 28, 2006
Medline	1966 - May 19, 2006
PubMed (Pre Medline)	Premedline[sb] last searched April 28, 2006
PsycINFO	Through April 28, 2006
TRIS Online (Transportation Research Information Service Database)	Through April 28, 2006

For the 2010 updated report, searches of the electronic databases cover the period of April 1, 2006 through November 6, 2010. One exception is noted for searches related to Key Question 2. Because we made a change to the inclusion criteria, our searches covered the period of time covered in the original report, through November 6, 2010. The databases searched are listed in Table 14.

Table 14: Electronic Databases Searched in the 2010 Update

Name of database	Date limits
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	April 1, 2006 – November 6, 2010
Cochrane Library	April 1, 2006 – November 6, 2010
Medline	April 1, 2006 – November 6, 2010
PubMed	April 1, 2006 – November 6, 2010
PsycINFO	April 1, 2006 – November 6, 2010
TRIS Online (Transportation Research Information Service Database)	April 1, 2006 – November 6, 2010

3.2.2. Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions about 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. These 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 it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), the full-length version of that article was obtained.

3.2.3. Inclusion and Exclusion Criteria

Each retrieved article was read in full to determine whether that article met predetermined, question-specific inclusion criteria. As was the case for the retrieval criteria, the inclusion and exclusion criteria for this evidence report were determined *a priori* in conjunction with FMCSA. These inclusion and exclusion criteria are presented in Appendix B.

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, is also presented in Appendix B.

3.3. Evaluation of Quality of Evidence

Rather than focus on the quality of the individual studies that an evidence base comprises, 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. Using this approach, which is described in Appendix C, we took into account not only the quality of the individual studies that make up 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 diabetes who require insulin are at increased risk for a motor vehicle accident) and a quantitative conclusion (e.g., When compared with individuals without diabetes, the relative risk for a motor vehicle crash among individuals with diabetes who require insulin is 1.37; 95% CI: 1.03–1.74; P <0.005). As shown in Table 15, we assigned a separate strength-of-evidence rating to each of 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 15: 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.
Minimally 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.
Insufficient	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. Requires 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. Requires 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. Requires 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 weak evidence. Likewise, quantitative effect-size estimates that are deemed to be stable are less likely to change significantly with the publication of new data than are unstable effect-size estimates.

3.4. Statistical Methods

The set of analytic techniques used in this report was extensive (Appendix C). In summary, random- and fixed-effects meta-analyses were used to pool data from different studies.[27-32] Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2. [31, 33-38] Whenever appropriate, heterogeneity was explored using meta-regression techniques.[39-41] Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative fixed- and random-effects meta-analyses. [42-48] The presence of publication bias was tested for, using the "trim and fill" method.[49-52]

We calculated several different estimates of treatment effectiveness. 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 the risk ratio (RR) or the odds ratio (OR). The

formulae for all four of these effect sizes and their variances are presented in Table 16. 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.[53]

Table 16: Effect-Size Estimates Used in Evidence Report and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
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)		
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 disorder who crashed; b = number of individuals without disorder who crashed; c = number of individuals with disorder who did not crash; d = number of individuals without disorder who did not crash.		

RR = rate ratio
OR = odds ratio
SMD = standardized mean difference
WMD = weighted mean difference

Section 4: Synthesis of Results

This section summarizes the findings of our analyses for each of the four key questions that we addressed.

4.1. Key Question 1: Are individuals with diabetes mellitus at increased risk for a motor vehicle crash when compared with comparable individuals who do not have diabetes?

4.1.1. Identification of Evidence Base

The identification of the evidence base for Key Question 1 is summarized in Figure 3. Our original searches yielded a total of 159 articles that appeared relevant to Key Question 1. Thirty-seven full-length articles were retrieved after applying the retrieval criteria, and 16 of them met the inclusion criteria. Our updated search for Key Question 1 yielded 190 articles. Ten full-length articles were retrieved, of which three were found to meet our inclusion criteria. Table B1 of Appendix B lists the articles that were retrieved but then excluded and provides rationale for their exclusion. Table 17 identifies all of the articles that met the inclusion criteria for Key Question 1. Studies are presented in reverse chronological order, with the most recent studies presented first. Detailed descriptions of each of the included studies for this question are presented in *Study Summary Tables* in Appendix E.

Figure 3: Development of Evidence Base Update for Key Question 1

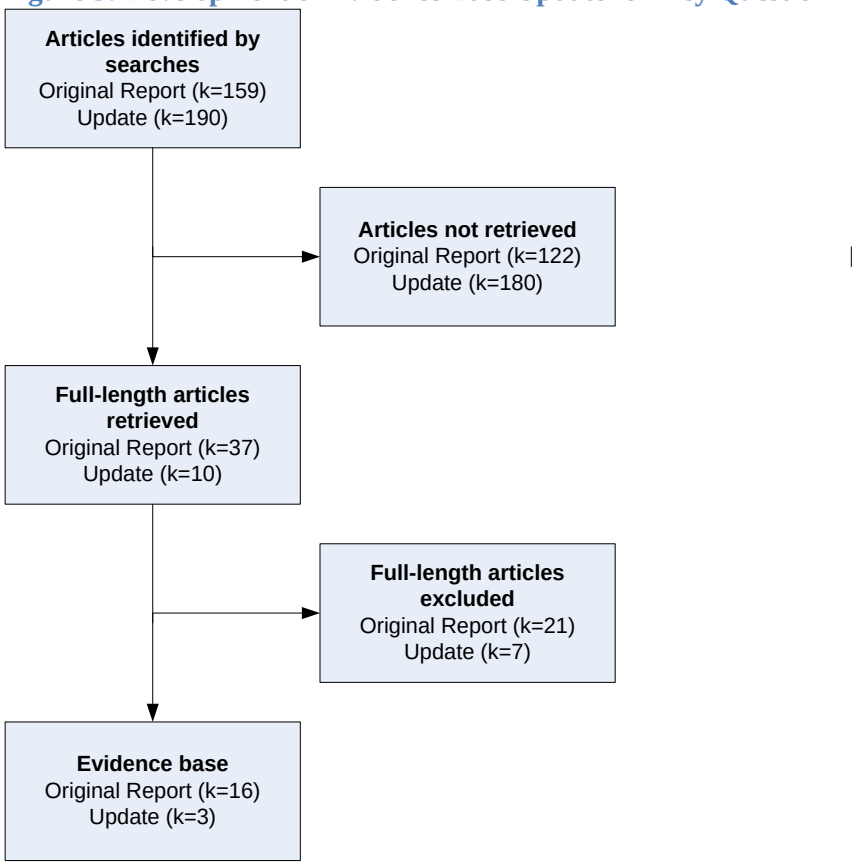


Table 17: Evidence Base for Key Question 1

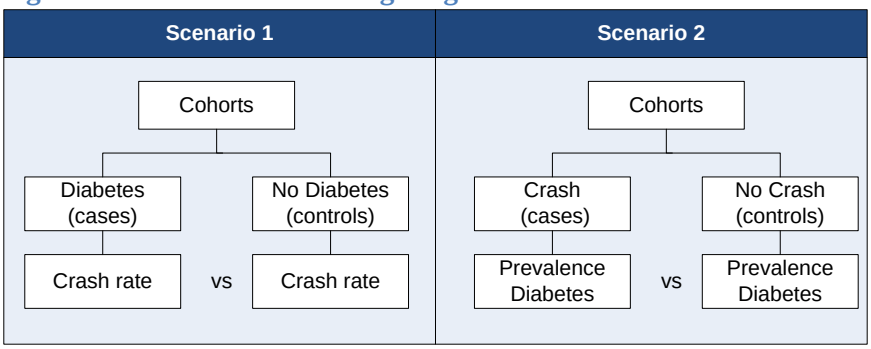
Reference	Year	Study Location	Country
2010 update			
Skurtveit et al.[54]	2009	Norway	Norway
Lonnen et al.[55]	2008	Exeter and East, Mid and North Devon	United Kingdom
Hemmelgarn et al.[56]	2006	Quebec	Canada
2006 report			
Cox et al.[15]	2003	Boston, Charlottesville, Chicago, Indianapolis, Louisville, St. Louis, Syracuse in USA; Amsterdam, Basel, Edinburgh and Mergentheim in Europe	U.S., Germany, Netherlands, Scotland, and Switzerland
Laberge-Nadeau et al.[57]	2000	Quebec	Canada
McGwin et al.[58]	1999	Alabama	U.S.
Gresset et al.[59]	1994	Quebec	Canada
Koepsell et al.[60]	1994	Washington	U.S.
Hansotia et al.[61]	1991	Wisconsin	U.S.
Stevens et al.[18]	1989	Belfast	Northern Ireland
Eadington et al.[19]	1988	Edinburgh	Scotland
Songer et al.[20]	1988	Pennsylvania	U.S.
De Klerk et al.[62]	1983	Western Australia	Australia
Davis et al.[63]	1973	Oklahoma	U.S.
Ysander et al.[64]	1970	Gothenburg	Sweden
Campbell et al.[65]	1969	Prince Edward Island	Canada
McMurray et al.[66]	1968	Washington	U.S.
Ysander et al.[67]	1966	Stockholm	Canada
Waller et al.[68]	1965	California	U.S.

4.1.2. Evidence Base

This subsection provides a brief description of the key attributes of the studies that constitute the evidence base for Key Question 1, including 16 studies in the original report and the three additional studies identified for the 2010 update. 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.

There are two primary approaches for investigating crash risk in individuals with diabetes (Figure 4). On the one hand, cohorts can be identified based on whether or not they have diabetes. In this scenario, crash rates among a group of individuals with diabetes (i.e., cases) are compared with crash rates among a group of individuals without diabetes). An alternative approach is to identify cohorts on the basis of whether or not they have had a crash, and then compare the prevalence of diabetes in the two groups. This is illustrated in Figure 4, below.

Figure 4: Scenarios for Investigating Risk of Crash in Diabetes



The key attributes of each included study are presented in Table 18.

Table 18: Key Study Design Characteristics that Address Key Question 1

Reference	Year	Design	Comparison	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
Skurtveit et al.[54]	2009	Population-based case-control study*	3.1 million individuals of whom 172,583 taking insulin, oral hypoglycemics, or both	No	Difference in crash rate (Scenario 1)	Motor vehicle accidents involving personal injuries, fatal or non-fatal, on Norwegian roads	No (registry records)
Lonnen et al.[55]	2008	Case-control study†	12,175 individuals with diabetes, compared with 394,139 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Car accidents that have been reported to the police where personal injury is caused to a person other than a driver or damage is caused to another vehicle, property or animal	No (state records)
Hemmelgarn et al.[56]	2006	Nested case-control study*	5,579 drivers who were involved in a crash (of these, 468 had diabetes), compared with 13,300 individuals not involved in a crash (there were 1,086 controls)	Yes	Difference in proportion of individuals with diabetes (Scenario 2)	Involvement of a cohort member as the driver in a motor vehicle crash in which at least one victim, not necessarily the driver, sustained bodily injury	No (provincial records)
Cox et al.[15]	2003	Case-control study†	673 individuals with diabetes compared with 363 individuals without diabetes	Yes	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	Yes (questionnaire)
Laberge-Nadeau et al.[57]	2000	Case-control study†	4,495 individuals with diabetes compared with 8,958 individuals without diabetes	Yes	Difference in crash rate (Scenario 1)	CMV driver crash where enrollee was driver	No (provincial records)
McGwin et al.[58]	1999	Case-control study*	249 individuals who had an at-fault crash compared with 454 individuals who had no crash	Yes	Difference in proportion of individuals with diabetes (Scenario 2)	At-fault crash where enrollee was driver	Yes (telephone questionnaire)

Reference	Year	Design	Comparison	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
Gresset et al.[59]	1994	Case-control study*	1,400 individuals injurious crash compared with 2,636 individuals no-crash	Yes	Difference in proportion of individuals with diabetes (Scenario 2)	Non-fatal crashes with minor bodily injury (not requiring hospitalization)	No (provincial records)
Koepsell et al.[60]	1994	Case-control study	234 individuals injured in crash compared with 446 not involved in crash	Yes	Difference of proportion of individuals with diabetes (Scenario 2)	Injurious motor vehicle crash where enrollee was driver	No (health insurance and police records)
Hansotia et al.[61]	1991	Case-control study†	484 individuals with diabetes compared with 30,420 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (state records)
Stevens et al.[18]	1989	Case-control study†	354 individuals with diabetes compared with 307 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	Yes
Eadington et al.[19]	1988	Case-control study†	187 individuals with diabetes compared with accident rate data obtained from Department of Transport Statistics and insurance claims	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	Yes
Songer et al.[20]	1988	Case-control study†	127 individuals with diabetes compared with 127 individuals without diabetes	Yes	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	Yes
De Klerk et al.[62]	1983	Case-control study†	8,623 individuals with diabetes compared with expected rates from entire population of Western Australia	No	Difference in crash rate (Scenario 1)	Injurious motor vehicle crash where enrollee was driver	No (hospital records)
Davis et al.[63]	1973	Case-control study†	108 individuals with diabetes compared with 1,650,245 non-diabetics	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (state records)
Ysander et al.[64]	1970	Case-control study†	219 individuals with diabetes compared with 219 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (state records)
Campbell et al.[65]	1969	Case-control study†	346 individuals with diabetes compared with 346 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (provincial records)
McMurray et al.[66]	1968	Case-control study†	7,646 individuals with diabetes compared with 1,600,000 individuals without	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (state records)

Reference	Year	Design	Comparison	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
			diabetes				
Ysander et al.[67]	1966	Case-control study†	256 individuals with diabetes compared with 256 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Injurious motor vehicle crash where enrollee was driver	No (government records)
Waller et al.[68]	1965	Case-control study†	287 individuals with diabetes compared with 922 individuals without diabetes	No	Difference in crash rate (Scenario 1)	Any motor vehicle accident where enrollee was driver	No (state records)

*A case-control study in which cases are defined according to whether individuals have experienced a crash and controls consist of a cohort of individuals who have not.
†A case-control study in which cases are defined according to the presence of diabetes and controls consist of a cohort of individuals who do not.

None of the 16 studies included in the 2006 report nor the three additional studies added to our evidence base in this update for Key Question 1 were prospective. Four studies (n=3 from the 2006 report; n=1 from the 2010 update) used a case-control study design that selected cohorts on the basis of crash involvement and compared the prevalence of diabetes among individuals who experienced a crash (cases) with those who did not (controls). Fifteen studies (n=13 from the 2006 report; n=2 from the 2010 update) used a case-control study design that selected drivers with diabetes (cases) and compared their risk with that of drivers who did not have the condition.

A design issue common with many risk assessment studies is the failure to control adequately for exposure. In this instance, the exposure variable of critical importance is the number of miles driven per unit time. If cases and controls are not well matched for driving exposure, then observed differences in risk may simply be the consequence of differences in total number of miles driven per unit time. In the original 2006 report, six studies[15, 20, 57-60] controlled for exposure, either matching driving patterns among cases and controls or adjusted for exposure using logistic regression. None of the three studies that were added to the evidence base with this update controlled for driving exposure (the most important confounder). Hemmelgarn et al.[56] in their study controlled for previous motor vehicle crash, age, sex, place of residence, and use of insulin using a logistic regression model, while Skurveit et al.[54] and Lonnen et al.[55] stratified risk by age and mode of therapy.

The three included studies in this update assessed the risk of diabetes associated with any motor vehicle accident in which the involved individual was a driver. However, some heterogeneity in the definition of a crash does exist between the studies. Hemmelgarn et al. analyzed crash data for individuals who were involved in a motor vehicle crash in which a victim, not necessarily the driver, sustained personal injury; Lonnen et al. analyzed data on motor vehicle crashes in which personal injury is caused to a person other than the driver or damage is caused to another vehicle, property or animal; while Skurveit et al. focused their attention on the risk of fatal or non-fatal motor vehicle crashes involving personal injuries.

Crash data in the included studies were obtained from both databases and questionnaires. In order for data from databases to be informative, relevant information must be precise. Since we have no way of determining how precise the information contained within any of the databases used to inform the studies included in this report is, 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 upon the honesty of the individual being questioned.

4.1.3. Quality of Evidence Base

There are a total of 19 studies in our evidence base. Our assessment of the quality of the evidence base for Key Question 1 is presented in Table 19. This assessment found that the quality of the included studies was low to moderate. Seven of the 19 studies were graded as moderate quality and the remaining 13 studies were graded as low quality. Although some of the included studies were well designed, executed, and documented, these studies used a case-control study design. Case-control studies, by virtue of their retrospective design, are susceptible to bias, meaning that even a perfectly designed and executed case-control study cannot be graded as high quality. Other important factors that differentiated moderate- from low-quality studies included poor reporting; failure to adjust for exposure differences in cases and controls; not matching study subjects in order to increase study efficiency, which can either result in underestimation or overestimation of risk among study groups; and making improper assumptions during the conduct of the studies.

Table 19: Quality of Studies that Address Key Question 1

Reference	Year	Quality Scale Used	Quality
Skurtveit et al.[54]	2009	Newcastle-Ottawa Quality Assessment Scale	Moderate
Lonnen et al.[55]	2008	Newcastle-Ottawa Quality Assessment Scale	Low
Hemmelgarn et al.[56]	2006	Newcastle-Ottawa Quality Assessment Scale	Moderate
Cox et al.[15]	2003	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Laberge-Nadeau et al.[57]	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
McGwin et al.[58]	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Gresset et al.[59]	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Koepsell et al.[60]	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Hansotia et al.[61]	1991	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Stevens et al.[18]	1989	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Eadington et al.[19]	1988	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Songer et al.[20]	1988	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
De Klerk et al.[62]	1983	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Davis et al.[63]	1973	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Ysander et al.[64]	1970	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Campbell et al.[65]	1969	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
McMurray et al.[66]	1968	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Ysander et al.[67]	1966	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Waller et al.[68]	1965	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low

4.1.4. Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that address Key Question 1 are presented in Table 20. The information included in this table demonstrates that currently available data that are directly generalizable to CMV drivers are extremely limited, as noted previously in the 2006 report. Only one out of 19 included studies (presented in the original report) evaluated crash risk in this

group of CMV drivers.[57] The results of this study are presented in the findings section below. The remaining 18 studies (including the three studies identified for the 2010 update) included individuals who held private motor vehicle licenses. We believe that included among these individuals were some CDL holders; however, the exact proportion of such drivers cannot be determined.

The generalizability of the findings of these studies to CMV drivers is limited by the lack of data specific to CMV drivers with diabetes and includes the following factors:

- Exposure levels are lower than would be seen in a CMV driver population. This will most likely lower the risk for a motor vehicle crash among the individuals included in the majority of the included studies.
- The proportion of women in the study samples is higher than would be seen in a CMV driver population.
- Four of the included studies (three studies from the original 2006 report, and one additional study for the 2010 update) were designed to determine the crash risk among the elderly (aged >65 years) who also had diabetes. Note that none of these four studies was excluded from our analyses because there is no upper age limit to being able to drive a CMV.[1] Also, inclusion of such studies gave us the potential for investigating the interaction between aging and diabetes and their combined influence on crash risk.

Table 20: Individuals with Diabetes Enrolled in Studies that Address Key Question 1

Reference	Year	Type of Diabetes	Number of Individuals with Diabetes Included (n)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	Driving Exposure	Percent White	Generalizability to Target Population
Skurtveit et al.[54]	2009	type 1/ type 2	483 (were involved in a crash)	18-69 years	NR	NR	NR	NR	NR	Unclear
Lonnen et al.[55]	2008	NR	12,175	>15 years	NR	54.5%	NR	NR	NR	Unclear
Hemmelgarn et al.[56]	2006	type 1/ type 2	468 (who were also involved in a crash)	Mean (cases) = 73.9 years Mean (controls) = 73.4 years	NR	NR	NR	NR	NR	No
Cox et al.[15]	2003	type 1/ type 2	673	Mean (T1)=42.4 years Mean (T2)= 56.7 years	Mean (T1)= 19.7 years Mean (T2)=11.3 years	T1=51 T2=61	NR	Mean (T1)=11,310 miles/year Mean (T2)=12,463 miles/year	NR	Low
Laberge-Nadeau et	2000	type 1/	1,063†	<66 years	NR	NR	100	NR	NR	Good

[1] Because these studies may represent a specific subgroup of studies, we ensured that we repeated our primary analysis with these studies removed as part of a series of sensitivity analysis (see below).

Reference	Year	Type of Diabetes	Number of Individuals with Diabetes Included (n)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	Driving Exposure	Percent White	Generalizability to Target Population
al.[57]		type 2								
McGwin et al.[58]	1999	type 1/ type 2	129	All ≥65 years	NR	≈50.0	NR	<4,000 miles/year ≈32% 4,000–7,999 miles/year ≈24% 8,000–13,000 miles/year ≈21% >13,000 miles/year ≈23%	74.5 %	Low
Gresset et al.[59]	1994	type 1/ type 2	121	All age 70	NR	NR	NR	NR	NR	Low
Koepsell et al.[60]	1994	type 1/ type 2	88	All ≥65 years	NR	50.0	NR	<5,000 miles/year: 44% 5,000–10,000 miles/year: 26% 10,000–15,000 miles/year: 20% >15,000 miles/year: 10%	95%	Low
Hansotia et al.[61]	1991	type 1/ type 2	484	Mean= 59.0 years	Mean= 8.7 years	57.2	NR	NR	NR	Unclear
Stevens et al.[18]	1989	type 1/ type 2	354	Mean=41 years (SD=13)	NR	61.3	NR	<8000 km/year: 32% 8000–17,700 km/year: 20% 17,701–26,000 km/year: 8% 26001–≥32,000 km/year: 9%	NR	Unclear
Eadington et al.[19]	1988	type 1 only	187	Mean= 52 years (Rng= 28–81)	Mean= 22 years (Rng=12–43)	63.9	NR	NR	NR	Unclear
Songer et al.[20]	1988	type 1 only	158	21–29 years: 22%	NR	55.7	NR	Mean=16.4 (SD=5.3)	97.5	Low

Reference	Year	Type of Diabetes	Number of Individuals with Diabetes Included (n)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	Driving Exposure	Percent White	Generalizability to Target Population
				30–39 years: 67% 40–49 years: 11%				years driving Mean=11,824 (SD=12,467) miles/year		
De Klerk et al.[62]	1983	type 1/ type 2	8,623	NR	NR	NR	NR	NR	NR	Unclear
Davis et al.[63]	1973	type 1/ type 2	108	NR	NR	NR	NR	NR	NR	Unclear
Ysander et al.[64]	1970	type 1/ type 2	219	18–20years: 2% 21–25years: 4% 26–30 years: 3% 31–40years : 15% 41-50 years: 21% 51–60 years: 30% >60 years: 25%	NR	NR	NR	1–4,999 miles/year: 17% 5,000–9,999 miles/year: 32% 10,000–19,999 miles/year: 29% >20,000 miles/year: 22%	NR	Low
Campbell et al.[65]	1969	type 1/ type 2	346	15–19 years: 2% 20–24 years: 3% 25–34 years: 6% 35–44 years : 9% 45-54 years : 18% 55–64: 25% >65 years: 37%	NR	81.9	NR	NR	NR	Unclear
McMurray et al.[66]	1968	type 1/type 2	7,646	NR	NR	NR	NR	NR	NR	Unclear
Ysander et al.[67]	1966	type 1/type 2	256	NR	NR	NR	NR	NR	NR	Unclear

Reference	Year	Type of Diabetes	Number of Individuals with Diabetes Included (n)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	Driving Exposure	Percent White	Generalizability to Target Population
Waller et al.[68]	1965	type 1/type 2	287	Mean (males)= 42.1 years Mean (females)= 38.1 years	NR	74.5	NR	Mean (males)= 12,600 miles/year Mean (females)= 5,200 miles/year	NR	Low

4.1.5. Findings for Key Question 1

The findings of the 19 studies (including the three new studies identified for the current 2010 update) that addressed Key Question 1 are presented in detail in the study summaries presented in Appendix E. As stated above, only one of the 19 studies included for Key Question 1 included a population of CMV drivers. The results of this single study are presented in section 4.1.5.1 below. None of the three additional studies identified for the 2010 update included a distinct population of CMV drivers or subgroup analyses that examined CMV drivers separately.

The evidence base for Key Question 1 is composed of two distinct types of case-control study. Four case-control studies compared the prevalence of diabetes among individuals who had been involved in a crash (cases) and a comparable group of individuals who had not (controls); scenario 2 from Figure 4. Fifteen case-control studies compared crash risk among individuals with diabetes (cases) with crash risk among a comparable group of individuals who do not have the disorder (controls); scenario 1 from Figure 4. Outcome data from the latter set of studies are presented as risk ratios[2], while outcome data from the former group of studies are presented as odds ratios[3].

Although both types of study may be used to address the same question from a qualitative perspective (does having diabetes increase crash risk), they differ from a quantitative perspective. In addition to quantitative differences in the two types of study, all four of the studies that compared the prevalence of diabetes among individuals who had been involved in a crash with the prevalence of diabetes among a comparable group of individuals who had not, included individuals who were over the age of 65. Consequently, we have analyzed data from the two different study types separately, and we place more weight on the findings of our analyses for data extracted from the larger set (n=15 studies) that compared crash risk among individuals with diabetes with crash risk among a comparable group of individuals who do not have the disorder.

4.1.5.1. Findings of the Single Case-Control Study Directly Generalizable to CMV License Holders (From the 2006 Report)

The information presented in this subsection is unchanged from the original report. Laberge-Nadeau et al.,[57] conducted a well-designed case-control study (**quality score=moderate**) in which they compared

[2] The risk of crash among individuals with diabetes divided by the risk of crash among comparable individuals who do not have diabetes
[3] The odds of having diabetes and having been involved in a crash divided by the odds of having diabetes if not involved in a crash

crash risk data from CMV drivers with diabetes in Québec, Canada who group-matched by age with a random sample of healthy permit holders. Data on permits, medical conditions, and crashes involving 13,453 permit holder–years in 1987–1990 were extracted from the files of the public insurer for automobile injuries in Québec. The investigators obtained additional health status data from the provincial public health insurer, and driving pattern and exposure data were obtained by means of a telephone survey.

Data were analyzed using multilevel negative binomial regression models in which each driver's medical status was nested within permit class. Mean yearly crash rates per driver with diabetes were compared with those occurring among drivers in good health using age and both quantitative and qualitative measures of driving exposure as covariates. The resulting risk ratios provided the marginal effect of belonging to the particular group in terms of relative crash risks, all other variables being equal. In some cases, exposure data from some CMV drivers could not be obtained. Consequently, Laberge-Nadeau et al. presented the findings of several models. In this evidence report, we focus on their model, which included exposure information (Table 21).

Table 21: Crash RRs and 95% CIs for Professional Drivers 1987–1990

Explanatory Variable	N=	Mean	RR	95% CI
Class AT				
Good health	1,736	0.17	1.00	Reference category
Diabetes without complications	369	0.13	0.81	0.58–1.14
Diabetes with complications	299	0.15	0.87	0.61–1.25
Diabetes treated with insulin	121	0.11	0.65	0.35–1.21
Class ST				
Good health	795	0.14	1.00	Reference category
Diabetes without complications	127	0.24	1.76*	1.06–2.91
Diabetes with complications	84	0.13	0.96	0.48–1.91
Diabetes treated with insulin	62	0.16	1.02	0.48–2.17
Distance driven (Class AT)				
<20,000 km	935	0.11	1.00	Reference category
20,001–50,000 km	836	0.17	1.55*	1.16–2.08
50,001–100,000 km	447	0.20	1.87*	1.33–2.64
>100,000 km	307	0.21	1.94*	1.26–2.99
Distance driven (Class ST)				
<20,000 km	497	0.13	1.00	Reference category
20,001–50,000 km	380	0.17	1.19	0.79–1.79
>50,000 km	191	0.19	1.40	0.82–2.38

*Statistically significant difference; AT=articulated truck; ST=straight truck

The increased crash risk for professional drivers with a permit to drive a straight truck (ST) and with uncomplicated diabetes that is not treated with insulin is surprising. First, the incidence of hypoglycemia is known to be higher among individuals treated with insulin than that among individuals treated with other agents or diet alone. Consequently, one might reasonably expect to see a higher risk ratio among individuals whose diabetes is controlled with insulin than is seen among individuals whose diabetes is controlled with oral hypoglycemic agents or diet alone (76 percent of individuals in this group were

taking a sulfonylurea). Second, one might expect that the same patterns of risk observed among drivers of straight trucks would also be observed among drivers of articulated trucks. This was not the case.

One possible reason for the unexpected results might be that employers of drivers of articulated trucks use stricter medical standards when hiring drivers. For example, the medical restrictions for diabetic truck drivers are more stringent in some Canadian provinces and for interstate travel in the United States.

For the analyses that looked at distance driven, Laberge-Nadeau et al. found that risk ratios for articulated truck (AT) drivers increased with distance driven. While the RRs for ST drivers were not significantly different from the reference category, there was a trend toward increasing RR with distance driven in this group as well.

While the findings of the study of Laberge-Nadeau et al. are informative, they do not, in and of themselves, provide sufficient evidence to allow an evidence-based conclusion about the relationship between the crash risk among CMV drivers and diabetes to be drawn. Such conclusions require the presence of confirmatory findings from other well-designed studies. As a consequence of the lack of direct evidence from CMV drivers, one must look to other evidence sources that have evaluated crash risk among much broader populations of drivers. An analysis of the results of such studies, while not necessarily directly generalizable to CMV drivers, will at least allow one the opportunity to draw evidence-based conclusions pertaining to the relationship between diabetes and the risk for a motor vehicle crash risk among drivers in general.

4.1.5.2. Findings of 15 Case-Control Studies that Compared Risk of Crash among Comparable Drivers with and without Diabetes

Fifteen included studies (13 from the 2006 report and two from the present review) reported on the ratio of the incidence of crash experienced by individuals with diabetes and the incidence of crash observed among a comparable group of individuals who did not have diabetes. The data are presented in Table 22.

Table 22: Crash Risk in Drivers with Diabetes Compared with Drivers without Diabetes

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
New evidence for 2010 update									
Skurviet et al. [54]	2009	Diabetes (insulin dependent) Diabetes (oral therapy) Controls	Person per year	NR	Yes	SIR =1.4 (1.2-1.6) SIR = 1.2 (1.0-1.3)	NR	Yes	Evidence that drivers that used insulin have a slightly increased risk of being involved in a road traffic accident

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
Lonnen et al.[55]	2008	Diabetes (all)	Annual accidents; rate per 100,000 that occurred over 5 years	0.043	No	0.58 (0.54-0.63)	<0.001	No	No evidence that insulin-treated patients as a group pose an increased risk of motor vehicle crash
		Diabetes (diet)		NR					
		Diabetes (oral therapy)							
		Diabetes (insulin)							
		Controls		0.73					
Evidence from 2006 report									
Cox et al.[15]	2003	Diabetes (type 1)	Percent of drivers experi-encing event in previous 2 years	19.00	No	RR=2.38 (1.41–3.78)	<0.001	Yes	Evidence that those drivers with both type 1 and type 2 diabetes are at increased risk for a motor vehicle accident
		Diabetes (type 2)		12.00	No	RR=1.5 (0.88–2.56)	0.135	No	
		Control		8.00	No				
Laberge-Nadeau et al.[57]	2000	Diabetes (all drivers)	Events per driver per year	0.16	Yes	RR=1.07 (0.88–1.30)	0.4976	No	No evidence that drivers with diabetes who drive commercial vehicles in Canada are at increased crash risk
		Control (all drivers)		0.15					
		Diabetes (AT-no comps)	Events per driver per year	0.13	Yes	RR=0.81 (0.58–1.14)	NS	No	No evidence that drivers with diabetes who drive articulated vehicles in Canada are at increased crash risk
		Diabetes (AT-comps)		0.15	Yes	RR=0.87 (0.61–1.25)	NS	No No	
		Diabetes (AT-insulin)		0.11	Yes	RR=0.65 (0.35–1.21)	NS	No	
		AT-control		0.17					
Laberge-Nadeau et al.[57]	2000	Diabetes (ST-no comps)	Events per driver per year	0.24	Yes	RR=1.76 (1.06–2.91)	<0.05	Yes	Evidence that drivers with diabetes who are not taking medication and drive straight trucks in Canada are at increased crash risk. No evidence that drivers with diabetes controlled with insulin or oral hypoglycemics are at increased crash risk.
		Diabetes (ST-comps)		0.13	Yes	RR=0.96 (0.48–1.91)	NS	No	
		Diabetes (ST-insulin)		0.16	Yes	RR=1.02 (0.48–2.17)	NS	No	
		ST-control		0.14					

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
Hansotia et al.[61]	1991	Diabetes (all) Control	Event rate per 1,000 person years	68.91 52.02	No	RR=1.32 (1.06–1.63)	0.0097	Yes	Evidence that drivers with diabetes are at increased crash risk
Stevens et al.[18]	1989	Diabetes (insulin dependent) Control	Events occurring over 5 years	82.00 75.00	No	RD=0.93 (0.66–1.32)	0.6783	No	No evidence that drivers with diabetes are at increased crash risk
Eadington et al.[19]	1988	Diabetes (insulin dependent) Control	Events per 1,000,000 miles	5.40 10.00	Yes	RR=0.54 (0.20–1.58)	0.2732	No	No evidence that drivers with type I diabetes are at increased crash risk
Songer et al.[20]	1988	Diabetes (insulin dependent) Control	Events per 100 drivers per 1,000,000 miles	10.40 3.91	Yes	RR=2.66 (0.80–7.67)	0.19	No	No evidence that drivers with type-I diabetes are at increased risk crash risk
De Klerk et al.[62]	1983	Diabetes (all) Control	Events occurring over 8 years	27.00 17.80	No	RR=1.52 (0.84–2.77)	0.1729	Unclear	No evidence that drivers with diabetes are at increased crash risk
Davis et al.[63]	1973	Diabetes (all) Control	Events per 100 drivers per year	7.40 7.10	No	RR=1.04 (0.37–2.91)	0.9470	No	No evidence that drivers with diabetes are at increased crash risk
Ysander et al.[64]	1970	Diabetes (all) Control	% of drivers experi-encing event during a mean period of 4.7 years	3.70 6.40	No	0.58 (0.25–1.40)	0.4279	No	No evidence that drivers with diabetes are at increased crash risk
Campbell et al.[65]	1969	Diabetes (all) Control	Total events per 5.5 years	91.00 53.00	No	RR=1.72 (1.18–1.40)	0.0043	Yes	Evidence that drivers with diabetes are at increased crash risk
McMurray et al.[66]	1968	Diabetes (all) Control	Events per 100 drivers over 6.75-year period	31.50 26.50	No	RR=1.19 (1.01–1.39)	0.0376	Yes	Evidence that drivers with diabetes are at increased crash risk

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
Ysander et al.[67]	1966	Diabetes (all) Control	Percent of drivers experi-encing event during a mean period of 4.7 years	5.00 7.70	No	RR=0.65 (0.17–3.38)	0.5290	Unclear	Point estimate only presented. No confidence interval nor P-value. Not enough information reported to calculate confidence intervals.
Waller et al.[68]	1965	Diabetes (all) Control	Events per driver per 1,000,000 miles	31.50	No	RR=1.78 (0.76 – 4.15)	<0.001	Yes	Evidence that drivers with diabetes are at increased crash risk

SIR: standardized incidence ratio

An initial review of the results of the 15 individual studies suggests that the available data on crash risk among individuals with diabetes is inconsistent. Eight studies provided evidence that diabetes is a risk factor for involvement in a motor vehicle accident [15, 20, 54, 61, 62, 65, 66, 68], while the results of the remaining studies found no such evidence.[18, 19, 55, 64, 66, 67]

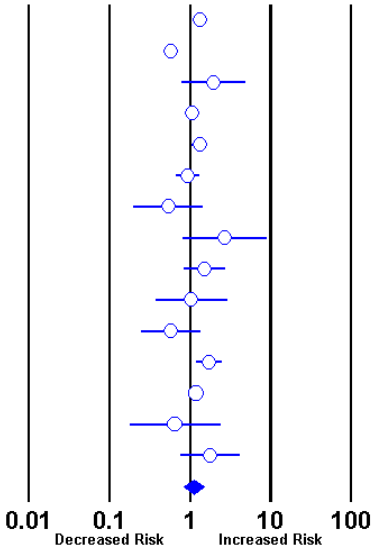
In addition to the differences in the qualitative findings of the included studies, there are likewise differences in the quantitative findings. Homogeneity testing revealed the presence of heterogeneity (differences in the results of different studies that cannot be explained by chance alone) in the findings of the 15 studies (I^2 =94.3%; Q=243.71, P=0.000). Refer to Figure 5, below.

Due to the heterogeneity between studies, we pooled the rate-ratio data of the 15 included studies using a random-effects meta-analysis. The random-effects model aims to determine a single weighted estimate of the risk ratio from the pooled results of the individual studies. This analysis yielded a summary risk ratio of **1.126 (95% CI: 0.847–1.497, P=0.415)**, consistent with a slight increase in risk of motor vehicle crash among drivers with diabetes when compared with the risk of motor vehicle crash among non-diabetic drivers. However, the effect estimate failed to reach statistical significance, having a confidence interval that includes a null value. Note: This finding is different from the finding observed in the 2006 report, where pooling of the original 13 studies yielded a summary risk ratio of 1.19 (95% CI: 1.08–1.31, P=0.0004). Thus, the addition of two recent studies (Skurviet et al. 2009, and Lonnen et al. 2008) eliminated the small significant effect previously observed.

Figure 5: Crash Risk in Drivers with Diabetes Compared with Drivers without Diabetes

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Skurtveit et al. 2009	1.329	1.196	1.477	5.266	0.000
Lonnen et al. 2008	0.580	0.540	0.623	-14.934	0.000
Cox et al. 2003	1.950	0.795	4.781	1.459	0.144
Laberge-Nadeau et al. 2000	1.070	0.880	1.301	0.680	0.497
Hansotia et al. 1991	1.320	1.058	1.647	2.459	0.014
Stevens et al. 1989	0.930	0.660	1.310	-0.415	0.678
Eadington et al. 1988	0.540	0.200	1.459	-1.215	0.224
Songer et al. 1988	2.670	0.803	8.881	1.602	0.109
de Klerk et al. 1983	1.520	0.840	2.750	1.384	0.166
Davis et al. 1973	1.040	0.370	2.922	0.074	0.941
Ysander et al. 1970	0.580	0.250	1.348	-1.266	0.205
Campbell et al. 1969	1.720	1.184	2.498	2.848	0.004
McMurray et al. 1968	1.190	1.007	1.406	2.044	0.041
Ysander et al. 1966	0.650	0.177	2.380	-0.650	0.515
Waller et al. 1965	1.790	0.763	4.198	1.339	0.181
	1.126	0.847	1.497	0.816	0.415

Heterogeneity test = I^2=94.093 Q=253.949 P=0.000



In the quality section of this report we mentioned some factors such as failure to match study subjects according to important variables and inappropriate assumptions that can lead to misleading results. We specifically want to call attention to criticisms brought forward by the UK DVLA[69] in response to the Lonnen et al. study. In their comment, the DVLA identified several important points that bear further discussion. They are:

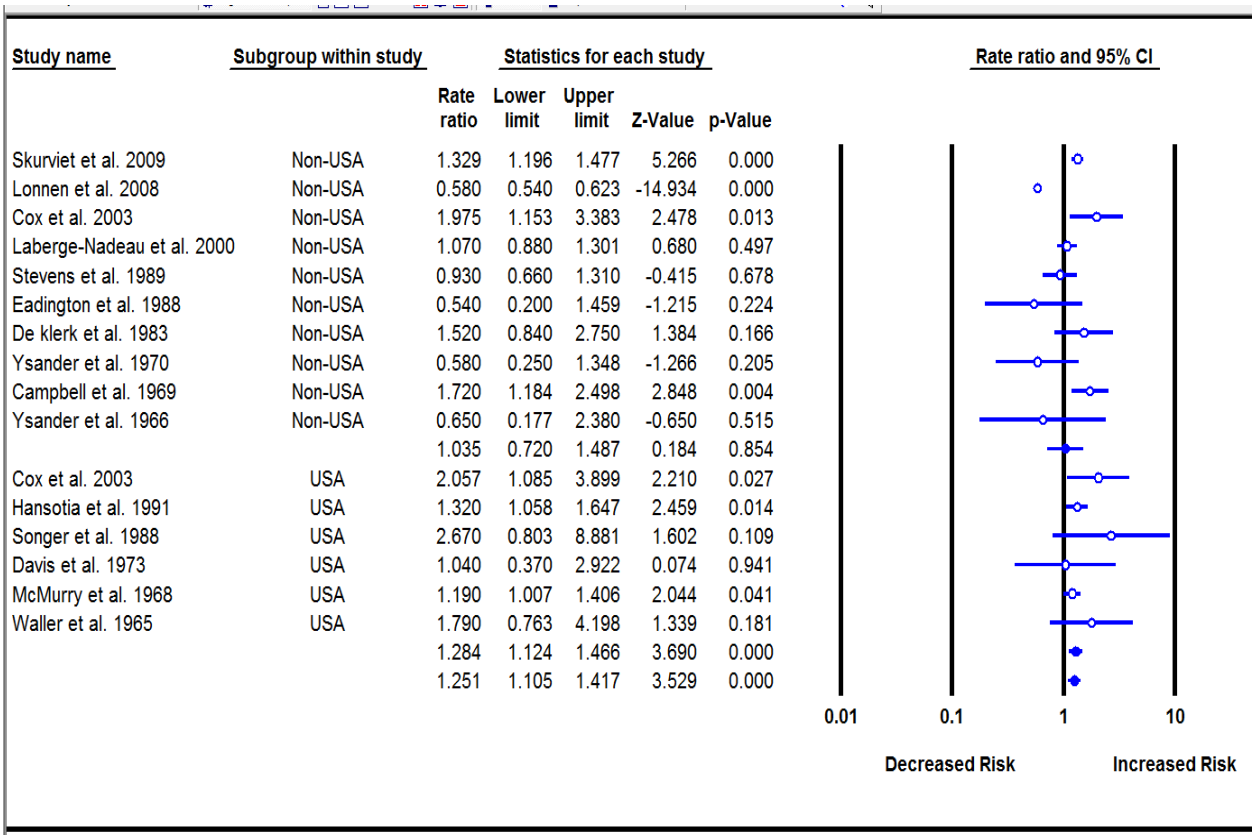
- In the non-diabetic population, the accident rate is heavily influenced by the number of young (especially male) drivers, as has been demonstrated by evidence from all studies of road accidents in the UK. While insulin-treated diabetes is not a condition that is limited to any single age group, its prevalence increases progressively with age; road accident data indicate that older, more experienced drivers have a much lower risk of accidents.
- An assumption was made that people with diabetes in the study held a driving license in the same proportion as the population without diabetes, but that might not have been the case. Young people with type 1 diabetes with previous severe hypoglycemic experience, or who are at risk of hypoglycemia or seizures, might have been reluctant to drive or perhaps might have delayed driving compared with their contemporaries.
- Most importantly, DVLA also argues that the risk of crash among individuals with diabetes was underestimated in the study due to the three-year medical review that is required for license renewal and removes those at highest risk.

This last point is an important point and has larger implications for the synthesis of data from many different countries. Given that many European countries, including the UK, perform license reviews of individuals with diabetes every three years, and licenses are revoked if there is a history of hypoglycemia unawareness or recurrent severe hypoglycemia, these study populations may not be as comparable (e.g.,

they are likely to have fewer of the higher-risk drivers with diabetes) to those from studies performed in the U.S., where no such requirements apply. As a result, we have rerun our synthesis of data to include a subgroup analysis of studies conducted in the United States, compared with studies conducted in other countries (non-U.S.).

The results of this subgroup analysis yield interesting findings. For the non-U.S. subgroup, the random-effects meta-analysis calculates a risk ratio of **1.035 (95% CI: 0.720-1.487; P=0.854)**, virtually no increase in crash risk among drivers with diabetes compared with individuals without diabetes. Contrary to this, the subgroup analysis including studies conducted in the U.S. results in a risk ratio of **1.284 (95% CI=1.124-1.466 P<0.0001)**, approximately a 24 percent increase in crash risk among drivers with diabetes compared with drivers without diabetes. These data are presented in Figure 6.

Figure 6: Crash Risk in Driver with Diabetes Compared with Drivers without Diabetes (Subgroup Analysis)



We next attempted to determine if any specific subgroups of drivers with diabetes were at an increased risk for crash. In particular, we wanted to compare the crash risk of insulin-treated drivers with diabetes to that of drivers with diabetes who control their condition with pharmacotherapy or diet alone. Five of the 13 included studies in the original report and one new study included in this update provided separate crash risk data solely for drivers who were insulin-treated. Consequently, it was possible to attempt to determine an estimate of the risk ratio associated with this subpopulation of drivers.

Included among the six studies was the study of Laberge-Nadeau et al. that specifically assessed crash risk among CMV drivers with diabetes. They presented data separately for articulated and straight truck drivers. We therefore made an assumption that the two data sets can be considered independent from one another because the two groups consisted of different sets of cases and controls (although sampled from the same database), and treated them as if they were two separate studies. Consequently, a total of seven data sets containing information on crash risk among drivers with insulin-dependent diabetes were available for analysis. Relevant outcome data from these seven data sets discussed above are plotted in Figure 7.

Homogeneity testing of these studies revealed that the data are heterogeneous (I^2=88.34; Q=68.61, P=0.000). That is, the findings of the seven studies differed by more than one would expect by chance alone. We did not attempt to explore the observed heterogeneity using meta-regression techniques because data from only seven studies were available to us. For statistical reasons, a minimum of 10 studies is required before the analysis of such data will become meaningful and valid.

The results of this meta-analysis (combining all data sets from the U.S. and non-U.S.-based studies) resulted in a risk ratio of **1.537 (95% CI: 0.603–3.915, P=0.368**). Again, the results of the overall summary of data were not significant. However, when looking at the U.S./non-U.S. subgroup analyses, we found that for studies conducted in the United States, there was a significant increase in crash risk for individuals treated with insulin when compared with drivers treated with oral medication and/or diet alone (**RR=2.753; 95% CI: 1.537–4.930, P=0.001**). No significant difference was found for the non-U.S. studies subgroup (**RR=1.036; 95% CI: 0.682–1.573, P=0.868**).

The primary risk factor for a crash among individuals with diabetes is traditionally thought to be hypoglycemia. There is a reasonably large body of literature showing that hypoglycemia occurs more often among individuals treated with insulin than among those treated by pharmacotherapy or diet alone. Thus, one might reasonably expect to observe that individuals with insulin-treated diabetes are at a particularly high risk for a motor vehicle crash when compared with individuals who control their diabetes by other means. The results of our meta-analysis present a mixed picture with respect to this contention, with increased risk being observed in the synthesis of studies conducted in the U.S., but not for the subgroup of non-U.S. studies.

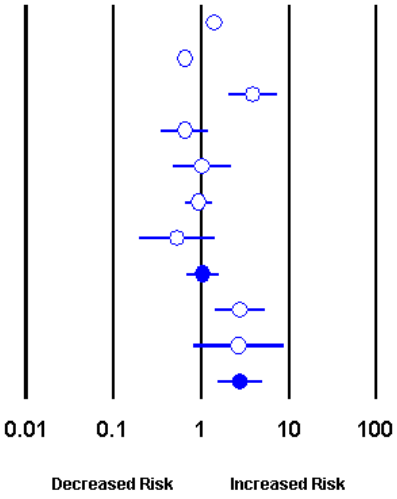
One possible explanation for this finding may relate to the three-year driving requirement for individuals with insulin-treated diabetes that exists in European countries and in the United Kingdom. As noted above, the effect of this requirement will be to remove individual drivers with diabetes who present the most significant risk for crash from the driving population. Thus we might expect to find a reduced or insignificant risk for crash in insulin-treated drivers in other countries, where this rule is in practice. No such requirement exists in the United States. Consistent with this hypothesis is the increased risk for crash that is observed in the U.S. subgroup of the meta-analysis presented in Figure 7. However, the U.S.

subgroup (looking at insulin-treated vs. other treatment/diet) includes the findings of only two studies; thus, a firm conclusion cannot be made at this time.

Laberge-Nadeau et al. has also argued that a process of self-selection occurs among individuals with insulin-treated diabetes and that the most severely affected individuals either restrict their driving or do not drive at all. As a consequence, crash-risk estimates determined for drivers with insulin-dependent diabetes are likely based on a subset of individuals with lower rates of hypoglycemia than would be seen in the larger universe of patients with insulin-treated diabetes. If this is true, indirect estimates of crash risk derived from published incidence rates for severe hypoglycemia that have not been weighted according to driving exposure (we are not aware of any such studies) will tend to overestimate the true crash rate for this group of individuals.

Figure 7: Results of Random-Effects Meta-Analysis (Insulin –Treated Diabetes Cohorts)

Study name	Comparison	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Skurtveit et al. 2009	Non-USA	1.400	1.205	1.627	4.395	0.000
Lonnen et al. 2008	Non-USA	0.653	0.540	0.789	-4.406	0.000
Cox et al. 2003	Non-USA	3.879	2.026	7.426	4.091	0.000
Laberge-Nadeau et al. 2000 (AT)	Non-USA	0.650	0.350	1.209	-1.361	0.173
Laberge-Nadeau et al. 2000 (ST)	Non-USA	1.020	0.480	2.169	0.051	0.959
Stevens et al. 1989	Non-USA	0.932	0.660	1.316	-0.400	0.689
Eadington et al. 1988	Non-USA	0.530	0.196	1.433	-1.251	0.211
		1.036	0.682	1.573	0.166	0.868
Cox et al. 2003 (US)	USA	2.782	1.429	5.416	3.010	0.003
Songer et al. 1988	USA	2.660	0.800	8.845	1.596	0.111
		2.753	1.537	4.930	3.406	0.001



4.1.5.3. Findings of Case-Control Studies that Compared Prevalence of Diabetes among Drivers Who Did and Did Not Crash

Three studies from the original report and one additional study included in the current update reported on the ratio of the odds of a driver having diabetes and being involved in a motor vehicle crash and the odds of having diabetes and not being involved in a motor vehicle crash (i.e., scenario 2 from Figure 4). All four studies focused on crash risk among individuals who were over the age of 65. The generalizability of the findings of these studies to CMV drivers is likely to be limited because individuals over age 65, especially women, are less likely to be seen driving a commercial vehicle truck. As a result, we consider the set of analyses that follow as secondary to the primary analysis presented in the previous section. We include this set of analyses in the main body of the evidence report because although they may be of

limited generalizability, the studies do offer the potential for gaining insight into the relative influence of different treatment regimens on crash risk.

In addition to reporting on relevant crash data for all individuals with diabetes (regardless of how it was controlled), each of the four studies included in the present set of analyses also reported on the odds ratio for several important subgroups that were classified by how diabetes was controlled: individuals who required insulin (all four studies), individuals who required pharmacotherapy (three studies), and individuals who maintained adequate glycemic control through a controlled diet alone (two studies). Relevant outcome data extracted from these four studies are presented in Table 23.

Table 23: Findings of Case-Control Studies that Compared Prevalence of Diabetes in Crash and Non-Crash Cohorts

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
New evidence for 2010 update									
Hemmelgarn et al.	2006	Diabetes (all)	Use of anti-diabetic therapy dispensed in the month prior to event date	0.08	Yes	RR= 1.02 (0.9-1.1)	NR	Yes	Evidence that drivers that used insulin have a slightly increased risk of being involved in a road traffic accident
		Control (all)		0.27					
		Diabetes (insulin monotherapy)		0.55	Yes	RR= 1.4 (1.0– 2.0)	NR	Yes	
		Control (insulin monotherapy)		0.27	Yes	RR=1.3 (1.0– 1.7)	NR	Yes	
		Diabetes (oral therapy combined)		0.44	Yes		NR	Yes	
		Controls (oral therapy combined)		0.27	Yes				
Evidence from 2006 report									
McGwin et al.	1999	Diabetes (all)	Difference in prevalence of diabetes in crash and non-crash cohorts	NR	Yes	OR=1.1 (0.7-1.9)	0.7325	No	No evidence that individuals with diabetes were at increased crash risk
		Control (all)		NR					
		Diabetes (diet control)		NR	Yes	OR=0.6 (0.2-2.5)	0.5216	No	
		Control (diet control)		NR					
		Diabetes (pharmacologic)		NR	Yes	OR=1.3 (0.7-2.2)	0.3283	No	
		Control (pharmacologic)		NR					
		Diabetes (insulin)		NR	Yes	OR=1.3 (0.6-2.9)	0.4410	No	
Gressert et al.	1994	Diabetes (all)	Difference in prevalence of diabetes in crash and non-crash	NR	No	OR=1.01 (0.80-1.27)	0.1936	Yes	No evidence that individuals with diabetes were at
		Control (all)		NR					
		Diabetes (insulin dependent)		NR	No	OR=1.13 (0.63-2.04)	0.6851	No	

Reference	Year	Cohort	Units	Crash Rate Data				Bottom Line	
				Rate (95% CI)	Exposure Adjusted ?	Effect Size* (95% CI)	P=*	Evidence of Increased Crash Risk	Conclusion
		Control (insulin. dependent)	cohorts						increased risk of crash
		Diabetes (non-insulin dependent)		NR	No	OR=0.99 (0.77-1.27)	0.9370	No	
		Control(insulin dependent)		NR					
Kopesell et al.	1994	Diabetes (all)	Difference in prevalence of diabetes in crash and non-crash cohorts	NR	No	OR=2.6 (1.4-4.7)	0.0016	Yes	Evidence that individuals with diabetes were at increased risk of crash
		Control (all)		NR					
		Diabetes (insulin)		NR	No	OR=5.8 (1.2-28.7)	0.0312	Yes	Evidence that individuals who controlled with insulin were at increased risk of crash
		Control (insulin)		NR					
		Diabetes (oral hypoglycemics)		NR	No	OR=3.1 (0.9-11.0)	0.0800	No	Unclear whether individuals who control diabetes with oral hypoglycemic are at increased risk
		Control (oral hypoglycemics)		NR					
		Diabetes (diet alone)		NR	No	OR=0.99 (0.4-2.4)	0.8332	No	No evidence that individuals who control diabetes with diet were at increased risk of crash
		Control (diet alone)		NR					

Note that rate ratio (RR) presented in the Hemmelgharn study is the same as an odds ratio (OR) in a logistic regression model.

Analysis of Data from All Individuals with Diabetes

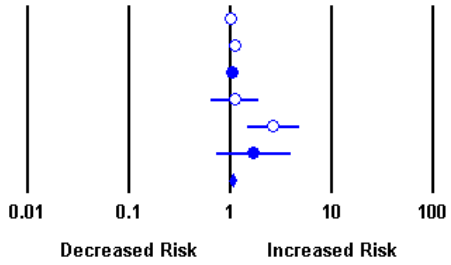
As stated above, all four included studies reported relevant crash risk data for individuals with diabetes regardless of how it was controlled. One included study found that individuals with diabetes are at increased risk for a motor vehicle accident. The remaining three studies, however, did not make this observation. Heterogeneity testing found that the differences in the findings of the four studies were greater than what one might expect by chance alone (**I^2=68.97%; Q=9.67, P=0.022**). We did not attempt to explore the observed heterogeneity using meta-regression because relevant data from only four studies are available at this time.

Pooling of the overall data using random-effects meta-analysis (Figure 8) found that drivers with diabetes are not overrepresented among samples of drivers who have experienced a crash (**odds ratio=1.052, 95%**

CI: 0.970–1.141; P=0.220). The results continue to be not significant after controlling for the country in which the study was conducted. For studies conducted in the U.S., the **odds ratio=1.684 (95% CI: 0.725–3.911; P=0.225**). Conversely, for studies conducted outside of the U.S., the **odds ratio=1.047 (95% CI: 0.966–1.136; P=0.265**).

Figure 8: Results of Meta-Analysis of Odds Ratio (Overall)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hemmelgarn et al. 2006	Non-USA	1.022	0.926	1.127	0.434	0.664
Gresset et al. 1994	Non-USA	1.105	0.956	1.278	1.348	0.178
		1.047	0.966	1.136	1.115	0.265
McGwin et al. 1999	USA	1.105	0.640	1.906	0.359	0.720
Koepsell et al. 1994	USA	2.611	1.440	4.734	3.162	0.002
		1.684	0.725	3.911	1.213	0.225
		1.052	0.970	1.141	1.227	0.220

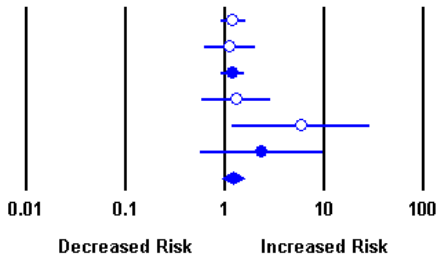


Analysis of Data from Individuals with Diabetes Controlled Using Insulin

All four studies included in the previous analysis presented data for a subgroup of enrollees who used insulin to control their diabetes. As was the case above, one of the four studies found that individuals with diabetes controlled using insulin were at an increased risk for hypoglycemia. However, the remaining three studies did not provide evidence of such a difference. Despite the apparent qualitative differences in the findings of the four studies, heterogeneity testing found that the results of these four studies were quantitatively homogeneous (**I^2=19.77; Q=3.74, P=0.291**). Consequently, we pooled the available data using a fixed-effects meta-analysis (Figure 9). Pooling of these data found that drivers with diabetes who controlled diabetes using insulin had a higher crash rate when compared with those who do not use insulin to control their diabetes (**odds ratio=1.212; 95% CI: 0.939–1.563, P=0.139**). However, the results of the overall analysis were not significant. The results of the U.S./non-U.S. subgroup analyses were, likewise, not significant. However, the trend for a larger odds ratio for studies conducted in the U.S. persisted. The results of the U.S. subgroup analysis were: **odds ratio=2.324; 95% CI: 0.554–9.741, P=0.249**. The results of the non-U.S. subgroup analysis were: **odds ratio=1.186; 95% CI: 0.916–1.536, P=0.196**. These results are shown in Figure 9, below.

Figure 9: Results of Fixed-Effects Meta-Analysis of Odds-Ratio Data (Insulin Users)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hemmelgarn et al. 2006	Non-USA	1.200	0.900	1.600	1.242	0.214
Gresset et al. 1994	Non-USA	1.130	0.626	2.039	0.406	0.685
		1.186	0.916	1.536	1.294	0.196
McGwin et al. 1999	USA	1.297	0.584	2.882	0.638	0.523
Koespell et al. 1994	USA	5.812	1.174	28.781	2.156	0.031
		2.324	0.554	9.741	1.153	0.249
		1.212	0.939	1.563	1.479	0.139

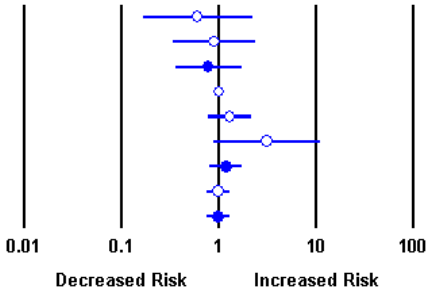


Analysis of Data from Individuals with Diabetes Controlled Using Pharmacotherapy or Diet Alone

Three of the four included studies presented data for separate subgroups of enrollees who controlled diabetes either by pharmacotherapy alone or by diet alone. None of them presented results suggesting that controlling diabetes by either of the two methods poses a significant increased rate of motor vehicle accident. Heterogeneity testing found that differences in findings of the three studies were not greater than those that one might expect to see by chance alone. [i.e. the results were homogenous (**I^2=12.779; Q=9.67, P=0.022**)]. Summary odds ratio estimate was **0.99 (95% CI=0.750-1.306, P=0.943),** which shows that odds of a motor vehicle crash among drivers with diabetes was increased by 8 percent; however, this finding was not significant. Subgroup analyses were also not significant. See Figure 10, below.

Figure 10: Results of Fixed-Effect Meta-Analysis of Odds-Ratio Data (Individuals using Oral Agents or Diet Alone)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
McGwin et al. 1999	diet	0.600	0.164	2.200	-0.771	0.441
Koespell et al. 1994	diet	0.896	0.336	2.388	-0.220	0.826
		0.775	0.354	1.694	-0.639	0.523
Hemmelgarn et al. 2006	oral hypoglycemics	1.000	0.900	1.111	0.000	1.000
McGwin et al. 1999	oral hypoglycemics	1.297	0.772	2.179	0.983	0.326
Koespell et al. 1994	oral hypoglycemics	3.096	0.869	11.028	1.744	0.081
		1.184	0.805	1.739	0.858	0.391
Gresset et al. 1994	Oral or diet	0.990	0.750	1.306	-0.071	0.943
		0.990	0.750	1.306	-0.071	0.943



4.1.6. Section Summary

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

A paucity of data from studies that enrolled CMV drivers with diabetes precludes one from determining whether CMV drivers with diabetes are at increased risk for a motor vehicle accident.

A single, moderate-quality case-control study evaluated crash risk among CMV drivers with diabetes as compared with comparable CMV drivers who did not have the disorder. This study was the only included study that specifically assessed crash risk among CMV drivers with diabetes. While the results of this Canadian study are directly applicable to CMV drivers in the United States, it is not a high-quality study and its findings have not been replicated. Consequently, one cannot draw an evidence-based conclusion pertaining to whether CMV drivers with diabetes are at an increased risk for a motor vehicle accident.

As a group, drivers with diabetes are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (strength of evidence: weak).

The magnitude of this increased risk is small and it is not statistically significant (risk ratio=1.126; 95% CI: 0.847–1.497; P=0.415). In other words, the crash risk for an individual with diabetes is 1.13 times greater than for a comparable individual who does not have the condition (stability of estimate of risk ratio: weak).

Subgroup analyses that take into account the country in which the study was conducted reveal differences between U.S. and non-U.S. conducted studies.

Fifteen case-control studies (overall quality=low) compared crash risk among drivers with diabetes (cases) and a comparable group of drivers who do not have the disorder (controls). Outcome data from this evidence base were presented in terms of a risk ratio. This is the ratio of the incidence of crash among drivers with diabetes (cases) and the incidence of crash among comparable drivers who do not have the disorder. Risk ratio values above 1 indicate that drivers with diabetes are at a higher risk for crash than drivers who do not have the disorder.

Quantitative analysis of outcome data from the 15 included studies found that the outcome data was heterogeneous (I^2 =94.16; Q=256.9, P=0.00). A random-effects meta-analysis in which these data were pooled found that the risk for crash among drivers with diabetes was 1.126 (95% CI: 0.847–1.497) times greater than the risk for crash among drivers who do not have the disorder. However, this risk ratio did not reach statistical significance.

A new analysis conducted in the present review that was not conducted in the 2006 report is a subgroup analysis that categorizes studies according to whether or not they were conducted in the U.S. The primary motivation for this analysis is that numerous non-U.S. countries employ a three-year license review criterion for individuals with IDDM. The U.S. does not have this requirement. A potential consequence of this license review process in other countries is the removal of individuals with IDDM who are at the largest risk for motor vehicle crash, which would have the effect of lessening or nullifying any potential risk that such individuals might present. Because the U.S. does not have a comparable

license review process for IDDM drivers (i.e., passenger car drivers), one might expect the observed risk for crash to be higher in the U.S. Our subgroup analyses support this suggestion. The risk ratios for the U.S. vs. non-U.S. subgroup analyses suggested that the risk for crash was higher in the U.S. (1.284 [95% CI: 1.124-1.466; P<0.0001]). The risk was significantly greater for individuals who treat their diabetes with insulin in the U.S. (2.753 [95% CI: 1.537-4.930; P=0.001]).

Whether drivers with type 1 or type 2 diabetes are overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.

Four case-control studies (overall quality=moderate), all of which enrolled individuals over the age of 65, compared the prevalence of drivers with diabetes among a cohort of drivers who had experienced a crash (cases) with the prevalence of drivers with diabetes among a cohort of drivers who had not experienced a crash (controls). Outcome data from this evidence base were presented as odds ratios. An odds ratio is the ratio of the odds of having diabetes and having been in a crash and the odds of having diabetes and having not been in a crash. Values above 1 indicate that drivers with diabetes are at a higher risk for crash than non-diabetics (the odds of having diabetes in the crash group are higher than the odds of having diabetes in the non-crash group).

Homogeneity testing found that the findings of the four included studies differed significantly. We did not attempt to explain the inconsistency in the findings of the four studies using meta-regression analysis due to the small size of the evidence base. Even though there was heterogeneity among these four studies, random-effects meta-analysis allows one to pool heterogeneous data by incorporating the observed between-studies variance into calculation of the summary effect-size estimate and its confidence intervals. The magnitude of effects shows that there was a slight increase in crash rates of drivers with diabetes when rate of crash is compared with that of those without diabetes (OR=1.260, 95% CI: 0.83-1.92; P=0.28) but the P value was insignificant. Consequently, we conclude that at the present time, it remains unclear whether drivers with diabetes are truly at increased risk of crash and not just by chance alone. More data are required before an evidence-based conclusion can be made.

Whether the subgroup of drivers with diabetes that is controlled by insulin is overrepresented in populations of drivers who have experienced a motor vehicle crash cannot be determined at this time.

All four of the case-control studies included in the previous analysis also attempted to determine whether drivers with diabetes treated using insulin are overrepresented among populations of drivers who have experienced a motor vehicle crash. These data were found to be homogeneous. Consequently, they were pooled using fixed-effects meta-analysis. As was the case in the previous analysis, the present analysis found that drivers with diabetes controlled using insulin tend to be overrepresented among samples of drivers who have experienced a crash. However, this overrepresentation is not statistically significant (OR=1.285, 95% CI: 0.91-1.82; P=0.159). Consequently, we conclude that at the present time, it remains unclear whether drivers with diabetes are overrepresented among populations of drivers who have experienced a motor vehicle crash. More data are required before an evidence-based conclusion about whether drivers with diabetes controlled by insulin are overrepresented among populations of drivers who have crashed.

4.2. Key Question 2: Is hypoglycemia an important risk factor for a motor vehicle crash among drivers with diabetes mellitus?

As stated in the Background section of this report, hypoglycemia is common among individuals who are receiving insulin or pharmacotherapy aimed at reducing blood glucose to near normal levels. Evidence suggests that hypoglycemia occurs more often in insulin-dependent diabetes than in diabetes that can be controlled through pharmacotherapy. Anecdotal evidence suggests that at least some accidents experienced by drivers with diabetes can be attributed to a hypoglycemic episode (see Table 8). Consequently, one would expect drivers with diabetes to be at an increased risk for a motor vehicle crash. Indeed, our analysis of crash risk data extracted from the 19 studies included in Key Question 1 provided some evidence to support this contention, showing that drivers with diabetes are at a slightly increased risk for a motor vehicle accident when compared with drivers who do not have the disorder.

As part of our evaluation of the evidence that addressed Key Question 1, we attempted to determine whether crash risk is higher among drivers who depend on insulin to control their blood glucose levels. The rationale for this analysis was that drivers who are insulin dependent are known to experience a higher incidence of hypoglycemia than drivers who control their diabetes using pharmacotherapy or by diet alone. Consequently, if hypoglycemia were the primary cause of the excess crash risk observed among drivers with diabetes, one would logically expect to observe higher crash rates among drivers with insulin-dependent diabetes. Our analyses demonstrated that, when considering studies conducted in the United States, drivers who depend on insulin to control their condition are at an increased risk for crash relative to individuals with diabetes who control their condition with oral medications and/or by diet alone. One probable explanation for this may be the increased risk for hypoglycemia (both mild and severe) that individuals who are treated with insulin face.

The purpose of Key Question 2 is to evaluate data from driving simulation studies and driving-related cognitive and psychomotor function studies to determine whether hypoglycemia is likely to be an important contributor to the excess crash risk observed among drivers with diabetes.

4.2.1. Identification of Evidence Base

The identification of the evidence base for Key Question 2 is summarized in Figure 11. The original search conducted in 2006 identified a total of 12 studies that met the criteria for inclusion. For the present update, our initial searches identified over 4,600 articles. After eliminating irrelevant articles based on examination of both titles and/or abstracts, 47 were retrieved. Following application of the slightly modified inclusion criteria applied in the current update, 15 additional articles were included.

As noted above, the inclusion criteria were modified slightly in the present report. Specifically, one of the original inclusion criteria of the 2006 report required that a study include a comparison group composed of comparable individuals with diabetes who did not have hypoglycemia at the time of testing. When this inclusion criterion was applied in conducting the 2006 review, only studies that included a separate control group were included. In the present update we have modified the interpretation of this criterion such that studies could be included if they performed testing in the same individuals in a euglycemic state, as well as a hypoglycemic state, thereby allowing for studies that employed a self-controlled study design (where individuals served as their own control) to be included. While having a separate control group is useful because it allows the investigators to control for learning and/or practice effects, this was not strictly necessary in order to access the clinical impact of hypoglycemia on cognitive and psychomotor

function. Because the inclusion criteria were modified slightly, our literature search covered the period 1964 through November 2010. Appendix B of this report presents the retrieval and inclusion criteria for this key question. Table B2 identifies articles that were retrieved but then excluded and provides the reason for their exclusion.

Figure 11: Development of Evidence Base Update for Key Question 2

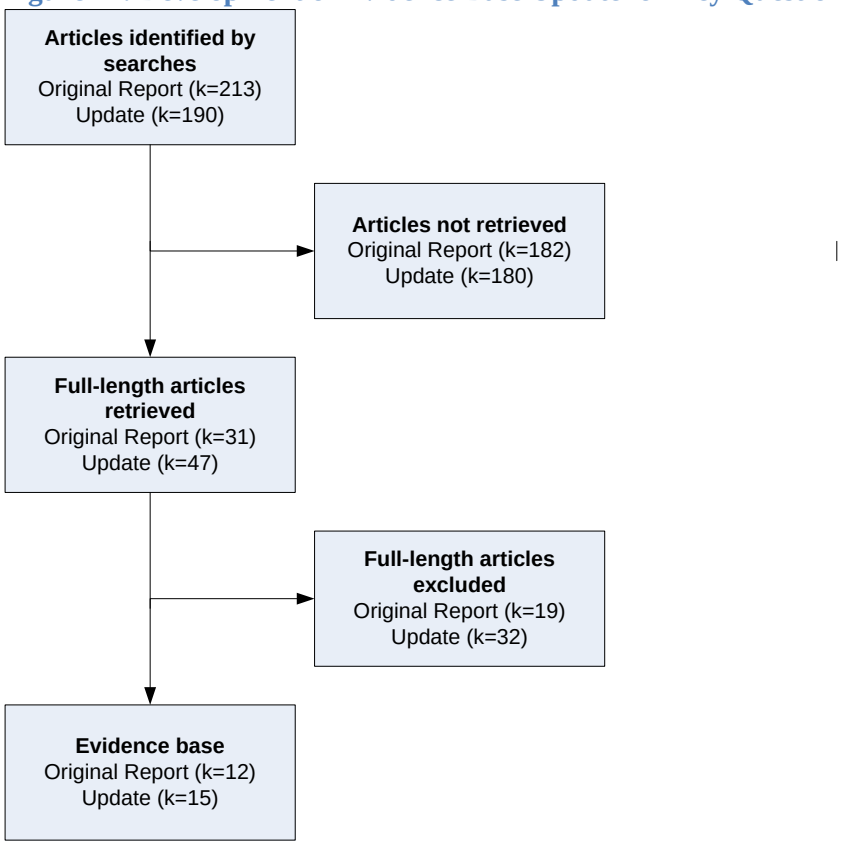


Table 24, below, identifies the 27 articles that met the inclusion criteria for Key Question 2 in the 2010 update.

Table 24: Evidence Base for Key Question 2

Reference	Year	Part of Key Question Addressed	Study Location	Country
Wright et al.[70]	2009	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Geddes et al.[71]	2008	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Zammitt et al.[72]	2008	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
McAulay et al.[73]	2006	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Cheyne et al.[74]	2004	Part b	Diabetes and Endocrine Center, Royal Bournemouth Hospital, Bournemouth, Dorset	England
Fanelli et al.[75]	2003	Part b	University of Perugia, Department of Internal Medicine, Perugia	Italy
Sommerfield et al.[6]	2003	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Strachan et al.[76]	2003	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Cox et al.[23, 77]	2000	Part a	University of Virginia Health System, Charlottesville, Virginia	U.S.
Lobmann et al.[78]	2000	Part b	Magdeburg University Medical School, Magdeburg	Germany

Reference	Year	Part of Key Question Addressed	Study Location	Country
Weinger et al.[24]	1999	Part b	Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts	U.S.
Ewing et al.[8]	1998	Part b	Department of Diabetes, Royal Infirmary of Edinburgh	Scotland
Draelos et al.[79]	1995	Part b	Joslin Diabetes Center, One Joslin Place, Boston MA	U.S.
Driesen et al.[80]	1995	Part b	University of Virginia Health System, Charlottesville, Virginia	US
Gold et al.[81]	1995	Part b	Department of Diabetes, Royal Infirmary, 1 Lauriston Place, Edinburgh EH3 9YW, Scotland	Scotland
Gonder-Frederick et al.[11]	1994	Part b	University of Virginia General Clinic Research Center, Charlottesville, Virginia	U.S.
Cox et al.[82]	1993	Part a	University of Virginia Health System, Charlottesville, Virginia	U.S.
Cox et al.[83]	1993	Part b	University of Virginia Health System, Charlottesville, Virginia	U.S.
Blackman et al.[84]	1992	Part b	University of Chicago, Illinois	U.S.
Lingenfelser et al.[85]	1992	Part b	Eberhard-Karls University, Tübingen	Germany
Widom et al.[86]	1990	Part b	Joslin Diabetes Center, New England Deaconess Hospital, Brigham and Women's Hospital, Boston, Massachusetts	U.S.
Hoffman et al.[87]	1989	Part a, b	University of Kansas School of Medicine, Wichita, Kansas	U.S.
Heller et al.[88]	1987	Part b	Nottingham University Medical School, Nottingham	England
Pramming et al.,[89]	1986		Steno Memorial Hospital, Gentofte	Denmark
Holmes et al.[90]	1986	Part b	University of Iowa, Iowa City, Iowa	U.S.
Herold et al.[91]	1985	Part b	University of Chicago, Illinois	U.S.
Holmes et al.[92]	1983	Part b	University of Iowa, Iowa City, Iowa	U.S.

4.2.2. Evidence Base

This subsection provides a brief description of the key attributes of the 27 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 F.

The primary characteristics of the 27 included studies that address Key Question 2 are presented in Table 25. All 27 studies were prospective. Some compared the response to induced hypoglycemia among drivers with diabetes with the response of drivers without the disease. For the purposes of this evidence report, however, such a comparison is superfluous. This is, in fact, the primary reason that we modified the inclusion criteria for this key question in the present report as described above. We are concerned only with the effects of hypoglycemia on simulated driving ability and/or cognitive or psychomotor function among individuals with diabetes. Consequently, we focus our attention on changes in driving ability or cognitive/psychomotor function that may occur among individuals with diabetes during controlled and differing levels of hypoglycemia when compared with euglycemic conditions. From this standpoint, all included trials are considered to be single-arm before–after studies in which samples of drivers with diabetes were assessed under euglycemic conditions and then again at various controlled levels of induced hypoglycemia.

Table 25: Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Study Design	Type of Diabetes	N=	Range of Conditions Tested	Relevant Outcomes Assessed
Simulated driving studies (Part A)						
Cox et al.[23, 77]	2000	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	37	Euglycemia (6.7 mmol/L) Hypoglycemia (2.2 mmol/L) †	Steering, braking, speed control
Cox et al.[82]	1993	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	25	Euglycemia (6.4 mmol/L) Hypoglycemia (2.4 mmol/L) †	Steering, speed control
Hoffman et al.[87]	1989	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	18	Euglycemia (5.6 mmol/L) Hypoglycemia (2.8 mmol/L)	Steering, speed control
Cognitive and psychomotor function studies (Part B)						
Wright et al.[70]	2009	Prospective single-arm multiple-condition (participants act as own control)	Type 1	16	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L) Euglycemia recovery (4.5 mmol/L)	Digit symbol substitution test (DSST) Trail Making B (TMB) test hypoglycemia symptom score hidden patterns card rotation cube comparison paper folding map memory maze tracing
Geddes et al.[71]	2008	Prospective single-arm multiple-condition	Type 1	16	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)	Four-choice reaction time test grooved pegboard tracing test pursuit rotor hand steadiness static balance hand grip digital symbol test hypoglycemia symptoms questionnaire
Zammitt et al.[72]	2008	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	36	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)	Trail Making B digit symbol substitution test choice reaction time (CRT)
McAulay et al.[73]	2006	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	16	Euglycemia (4.5 mmol/L) Hypoglycemia (2.6 mmol/L)	Test of everyday attention Raven's Standard Progressive Matrices
Cheyne et al.[74]	2004	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	17	Euglycemia (4.5 mmol/L) Hypoglycemia (2.8 mmol/L)	Digital symbol task Trail Making Task B four-choice reaction time visual change detection Hazard Perception Test Symptoms of Hypoglycemia
Fanelli et al.[75]	2003	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	11	Euglycemia (5.5 mmol/L) Hypoglycemia (2.4 mmol/L)	Trail Making Part A Trail Making Part B backward digit span verbal memory test paced auditory serial addition task (PASAT)
Sommerfield et al.[6]	2003	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	16	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)	Immediate and delayed verbal memory immediate and delayed visual memory

Reference	Year	Study Design	Type of Diabetes	N=	Range of Conditions Tested	Relevant Outcomes Assessed
						Trail Making B Test digit symbol test
Strachan et al.[76]	2003	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	15	Euglycemia (5.0 mmol/L) Hypoglycemia (2.6 mmol/L)	Cognitive test digit symbol task Trail Making Test B auditory information processing test auditory event-related potentials test
Lobmann et al.(90)	2000	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	12	Euglycemia (6.1 mmol/L) Hypoglycemia (2.6 mmol/L)†	selective attention task (custom)
Weinger et al.(91)	1999	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	60	Euglycemia (6.7 mmol/L) Hypoglycemia (2.2 mmol/L) †	Reaction time (MCRTA) attention (DVT) selective attention, mental flexibility, visual spatial skills (TMT A and B)
Ewing et al.[8]	1998	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	16	Euglycemia (5.0 [SD=0.3] mmol/L) Hypoglycemia (2.6 [SD=0.2] mmol/L)	General cognitive function (digit symbol test; Trail Making B Test) visual acuity & contrast sensitivity visual information processing (inspection time; visual change detection; visual movement detection) hypoglycemia symptom questionnaire
Draelos et al.[79]	1995	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	42	Euglycemia (8.9 mmol/L) Hypoglycemia (8.9, 5.6 and 2.2 mmol/L) Hyperglycemia (8.9, 14.4 and 21.1 mmol/L)	Visual reaction time (RT) digit vigilance test Trail Making Test Part B word recall task digit sequence learning test verbal fluency test
Driesen et al.[80]	1995	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	25	Euglycemia (NR) Hypoglycemia (2.5 mmol/L)†	Reaction time (NES2)
Gold et al.[81]	1995	Prospective double-arm multiple-condition (there were participants and controls) Note: Controls differed from participants in terms of history of hypoglycemic unawareness, not type 1 diabetes. Both groups had type 1 diabetes.	Type 1	20	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)	Paced auditory serial addition test (PASAT) digit symbol substitution test Trail Making B rapid visual information processing (RVIP)
Gonder-Frederick et al.[11]	1994	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	26	Euglycemia, base level (6.4 mmol/L) Hypoglycemia, mild (3.6 mmol/L) Hypoglycemia, moderate (2.6 mmol/L) Euglycemia, recovery (6.3	Writing name and address (routine task) coin-flipping [easy & hard] (routine task) Serial subtractions twos and sevens verbal fluency

Reference	Year	Study Design	Type of Diabetes	N=	Range of Conditions Tested	Relevant Outcomes Assessed
					mmol/L)	Trail Making B
Cox et al.[83]	1993	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	17	Euglycemia (4.5 mmol/L) Hypoglycemia (2.8 mmol/L)	Digital symbol task Trail Making Task B four-choice reaction time visual change detection hazard perception test symptoms of hypoglycemia
Blackman et al.[84]	1992	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	10	Euglycemia (5.6 to 4.4 mmol/L) Hypoglycemia (2.5 mmol/L)†	Reaction time
Lingenfelser et al.[85]	1992	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	10	Euglycemia (5.5 mmol/L) Hypoglycemia (2.2 mmol/L)†	Selected cognitive and psychomotor skills (PSE-syndrome-test) reaction time (VRT)
Widom et al.[86]	1990	Cross-sectional physiologic and neuropsychologic evaluation	Type 1	27	Hypoglycemia (2.2 mmol/L)	Attention memory visual-spatial skills visual-motor skills global cognition
Hoffman et al.[87]	1989	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	18	Euglycemia (5.6 mmol/L) Hypoglycemia (2.8 mmol/L)	Reaction time (visually cued reaction timer) vigilance and motor control (pursuit rotor) selective attention, mental flexibility, visual spatial skills (TMT A and B)
Heller et al.[88]	1987	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	15	Euglycemia (4.5 mmol/L) Hypoglycemia (2.5 mmol/L)†	Reaction time
Holmes et al.[90]	1986	Prospective single-arm multiple-condition (participants act as own controls)	Type 1	24	Euglycemia (6.1 mmol/L) Hypoglycemia (3.1 mmol/L)	Simple and complex reaction times
Pramming et al.[89]	1986	Neuropsychological evaluation	Type 1	16	Hypoglycemia (6.3 – 1.8 mmol/L)	Simple motor tests memory tests control tests
Herold et al.[91]	1985	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	12	Euglycemia (6.1–4.7 mmol/L) Hypoglycemia (2.5 mmol/L)†\	Reaction time (custom system)
Holmes et al.[92]	1983	Prospective single-arm multiple-condition* (participants act as own controls)	Type 1	12	Euglycemia (6.1 mmol/L) Hypoglycemia (3.1 mmol/L)	Memory tasks (digit supraspan; Rey Auditory Verbal Learning Test attention tasks (MFFT; delayed reaction time) visual spatial task (BVRT) academic tasks (NDRT; mathematical computations)

* Study compared cognitive function in diabetics and non-diabetic controls. For Key Question 2, we are only interested in the diabetic cohort. Thus for the purposes of this question, this study is a single-arm multiple-condition study;
† Cognitive or psychomotor function assessed at several other conditions falling within these levels were assessed

BVRT=Benton Visual Retention Task; DVT=Digit Vigilance Task; MCRTA=Multiple-Choice Reaction Time Apparatus; MFFT=Matching Familiar Figures Test; NDRT=Nelson Denny Reading Test; NES=Neurobehavioral Evaluation System; PSE=portosystemic encephalopathy; TMT A and B= Trial Making Test Parts A and B; VRT=Vienna Reaction Timer;

4.2.3. 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 26. This assessment found that the quality of all of the included studies was in the low to moderate range, with all but one study being graded as moderate quality.

Table 26: Quality of Studies (Key Question 2)

Reference	Year	Quality Scale Used	Quality
Simulated driving studies			
Cox et al.[23, 77]	2000	Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies(101)	Moderate
Cox et al.[82]	1993	Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies(101)	Moderate
Hoffman et al.[87]	1989	ECRI Quality Scale III-Before After Study	Moderate
Cognitive or psychomotor function studies			
Wright et al.[70]	2009	ECRI Quality Scale 1 – Controlled Trials	Moderate-High
Geddes et al.[71]	2008	ECRI Quality Scale 1 – Controlled Trials	Low-Moderate
Zammitt et al.[72]	2008	ECRI Quality Scale 1 – Controlled Trials	Moderate
McAulay et al.[73]	2006	ECRI Quality Scale 1 – Controlled Trials	Low-Moderate
Cheyne et al.[74]	2004	ECRI Quality Scale 1 – Controlled Trials	High
Fanelli et al.[75]	2003	ECRI Quality Scale 1 – Controlled Trials	Moderate
Sommerfield et al.[6]	2003	ECRI Quality Scale 1 – Controlled Trials	Moderate-High
Strachan et al.[76]	2003	ECRI Quality Scale 1 – Controlled Trials	Low-Moderate
Lobmann et al.[78]	2000	ECRI Quality Scale III-Before After Study	Moderate
Weinger et al.[24]	1999	ECRI Quality Scale III-Before After Study	Moderate
Ewing et al.[8]	1998	ECRI Quality Scale 1 – Controlled Trials	Low-Moderate
Draelos et al.[79]	1995	ECRI Quality Scale 1 – Controlled Trials	High
Driesen et al.[80]	1995	ECRI Quality Scale III-Before After Study	Low
Gold et al.[81]	1995	ECRI Quality Scale 1 – Controlled Trials	Low-Moderate
Gonder-Frederick et al.[11]	1994	ECRI Quality Scale 1 – Controlled Trials	Moderate-High
Cox et al.[83]	1993	ECRI Quality Scale III-Before After Study	Moderate
Blackman et al.[84]	1992	ECRI Quality Scale III-Before After Study	Moderate
Lingenfelser et al.[85]	1992	ECRI Quality Scale III-Before After Study	Moderate
Widom et al.[86]	1990	ECRI Quality Scale III-Before After Study	Moderate
Hoffman et al.[87]	1989	ECRI Quality Scale III-Before After Study	Moderate
Heller et al.[88]	1987	ECRI Quality Scale III-Before After Study	Moderate
Holmes et al.[90]	1986	ECRI Quality Scale III-Before After Study	Moderate
Pramming et al.[89]	1986	ECRI Quality Scale III-Before After Study	Moderate
Herold et al.[91]	1985	ECRI Quality Scale III-Before After Study	Moderate
Holmes et al.[92]	1983	ECRI Quality Scale III-Before After Study	Moderate

4.2.4. Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that address Key Question 2 are presented in Table 27. None of the included studies examined task performance in a population of CMV drivers. Consequently, the degree to which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to professional drivers is unclear. Another important limitation of the generalizability of the included studies to CMV drivers is that no study enrolled individuals with type 2 diabetes. Given that the prevalence of type 2 diabetes in the general population is considerably higher than that of type 1 diabetes (see Background section), and the fact that it is not clear that the effects of hypoglycemia on cognitive performance, psychomotor function, and driving performance among individuals with type 2 diabetes are comparable, the limitations of this evidence base are clear.

Table 27: Characteristics of Enrolled Patients (Key Question 2)

Reference	Year	Diabetes Type	Number of Individuals with Diabetes Included (n=)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	HBA1c (percent)	IQ	BMI	Generalizability to Target Population
Driving performance studies											
Cox et al.[23, 77]	2000	Type 1	37	Mean=35.9 (SD=7.1) years Range=NR	Mean=17.5 (SD=10.0) years Range=NR	43.2	NR	Mean=8.5 (SD=1.8) Range=NR	NR	Mean=35.3 (SD=7.3) Range=NR	Unclear
Cox et al.[82]	1993	Type 1	25	Mean=35.9 (SD=14.2) years Range=NR	Mean=14.6 (SD=10.5) years Range=NR	48.0	NR	Mean=10.8 (SD=2.9) Range=NR	NR	NR	Unclear
Hoffman et al.[87]	1989	Type 1	18	Mean=29.3 (SD=1.2) years Range=NR	Mean=7.7 (SD=1.6) years Range=NR	44.4	NR	Mean=6.9 (SD=1.3) Range=NR	NR	NR	Unclear
Cognitive and psychomotor function studies											
Wright et al.[70]	2009	Type 1	16	Median=28 years Range=25-37.5 years	Median=10 years Range=4.2-19 years	43.75	NR	NR	NR	26.4 (SD=4.01)	Unclear
Geddes et al.[71]	2008	Type 1	16	Mean=40.0 years Range=36-42.8 years	Mean=15 years Range=6-25 years	50.0	NR	Mean=8.2 (SD=0.6) Range=NR	NR	NR	Unclear
Zammitt et al.[72]	2008	Type 1	36	NR	IHA Group: Median=33.5 Range=22-43 NHA Group: Median=29.0 Range=19-44	NR	NR	NR	NR	NR	Unclear
McAulay et al.[73]	2006	Type 1	16	Median=25.5 years Range=18-39 years	Median=8 years Range=2.5-15 years	NR	NR	7.7 (SD=1.0)	109	24.1 (SD=1.8)	Unclear
Cheyne et al.[74]	2004	Type 1	17	Mean=35.0 years Range=21-46 years	Mean=19 (SD=12) years	82.4	NR	Mean=8.1 (SD=1.4) Range=NR	NR	NR	Unclear

Reference	Year	Diabetes Type	Number of Individuals with Diabetes Included (n=)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	HBA1c (percent)	IQ	BMI	Generalizability to Target Population
Fanelli et al.[75]	2003	Type 1	11	Mean=29 (SD=2.4) years Range=NR	Mean=12 (SD=2.7) years Range=NR	54.5	NR	Mean=6.6 (SD=0.3), Range=NR	NR	Mean=21.8 (SD=0.7), Range=NR	Unclear
Sommerfield et al.[6]	2003	Type 1	16	Median=28.5 years Range=20 - 38.2 years	Median=4.5 years Range=1.2-8.4 years	56.25	NR	8.2	NR	23.9	Unclear
Strachan et al.[76]	2003	Type 1	15	Mean=26.5 years	Mean=11.1 (SD=6.6) years	73.33	NR	8.8 (SD=2.0)	Above average intelligence	22.9 (SD=1.7)	Unclear
Lobmann et al.[78]	2000	Type 1	12	Mean=31.0 (SD=7) years Range=20–43 years	Mean=7.8 (SD=8.6) years Range=1–29 years	58.3	NR	Mean=7.38 (SD=1.8) Range=NR	NR	Mean=24.2 (SD=3.9) Range=NR	Unclear
Weinger et al.[24]	1999	Type 1	60	Mean=33.0 (SD=9) years Range=NR	Mean=9.0 (SD=3) years Range=NR	50.0	NR	Mean=8.7 (SD=1.0) years Range=NR	NR	NR	Unclear
Ewing et al.[8]	1998	Type 1	16	Mean=26.9 years Range=18-47 years	Mean=8.8 years Range=2-17 years	75.0	NR	Mean=8.5 (SD=1.3) Range=NR	National Adult Reading Test: 18.8 (SD=7.6) Alice Heim 4 Test: 92.3 (SD=14.6) Both indicate above-average intelligence	NR	Unclear
Draelos et al.[79]	1995	Type 1	42	Mean=29.0 (SD=8.0) years Range=NR	Mean=8.7 (SD=3.5) years Range=NR	47.6	NR	Historic HbA1: Mean=10.6 (SD=2.3) Range=NR	Verbal IQ Mean=103 (SD=11)	NR	Unclear

Reference	Year	Diabetes Type	Number of Individuals with Diabetes Included (n=)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	HBA1c (percent)	IQ	BMI	Generalizability to Target Population
								Study HbA1: Mean=10.0 (SD=2.0) Range=NR			
Driesen et al.[80]	1995	Type 1	25	Mean=35.5 (SD=14) years Range=19–67 years	Mean=14.3 (SD=10.6) years Range=2–36 years	48.0	NR	Mean=10.6 (SD=0.58) Range=6–16.7	Mean=109 (SD=11) Range=90–137	NR	Unclear
Gold et al.[81]	1995	Type 1	30	Group A: Mean=37.4 (SD=5.1) years Range=NR Group B: Mean=35.0 (SD=7.7) years Range=NR	Group A: Mean=17.9 (SD=7.8) years Range=NR Group B: Mean=12.8 (SD=4.4) years Range=NR	NR	NR	Group A: Mean=10.3 (SD=2.2) Range=NR Group B: Mean=9.7 (SD=1.0) Range=NR	Group A: Mean NART score=36.3 (SD=6.5) Mean WAIS-R IQ=109, AH4 score=86.4 (SD=15.3) Group B: Mean NART score=35.4 (SD=10.1), Mean WAIS-R IQ=108, Mean AH4 score=78.3 (SD=13.0)	Group A: Mean=24.2 (SD=3.0) years Range=NR Group B: Mean=25.6 (SD=2.7) years Range=NR	Unclear
Gonder-Frederick et al.[11]	1994	Type 1	26	Mean=35.9 (14.2) years Range=19-67 years	14.6 (SD=10.5) years Range= 2-36 years	46.2	NR	Mean=10.8 (SD=2.9) Range= 6.1-16.7	Mean= 108.5 (SD=11.7) Range=90-137	NR	Unclear
Cox et al.[83]	1993	Type 1	10	Mean=34 Range=NR	Mean=18 years Range=NR	40.0	NR	Mean=9.8 Range=NR	NR	NR	Unclear
Blackman et	1992	Type 1	14	Mean=29.5	Mean=15.2	42.8	NR	Mean=11.0	NR	Mean=23.8	Unclear

Reference	Year	Diabetes Type	Number of Individuals with Diabetes Included (n=)	Age Distribution	Duration of Diabetes	Percent Male	Percent CMV Drivers	HBA1c (percent)	IQ	BMI	Generalizability to Target Population
al.[84]				(SE=1.6) years Range=NR	(SE=2.0) years Range=NR			(SE=0.5) Range=NR		(SE=0.5) Range=NR	
Lingenfelser et al.[85]	1992	Type 1	10	Mean=38.5 (SD=11.2) years Range=NR	Mean=10.5 (SD=4.3) years Range=NR	40.0	NR	Mean=9.5 (SD=1.1) Range=NR	NR	NR	Unclear
Widom et al.[86]	1990	Type 1	17	Nondiabetic: 27 (SD=1) Good glycemic control: 27 (SD= 2) Poor glycemic control: 22 (SD =1)	-- 7 (SD=1) years 12 (SD=2) years	47.1	NR	--- 8.0 (SD=0.2) 11.8 (SD=0.4)	NR	23 (SD =1) 3 (SD= 1) 25 (SD =3)	Unclear
Hoffman et al.[87]	1989	Type 1	18	Mean=29.3 (SD=1.2) years Range=NR	Mean=7.7 (SD=1.6) years Range=NR	44.4	NR	Mean=6.9 (SD=1.3) Range=NR	NR	NR	Unclear
Heller et al.[88]	1987	Type 1	15	Mean=36.0 (SE=3.0) years Range=NR	Mean=9.9 (SE=0.5) years Range=NR	80.0	NR	Mean=9.3 (SE=0.3) Range=NR	NR	NR	Unclear
Holmes et al.[90]	1986	Type 1	24	Mean=21.3 (SD=NR) years Range=18–35 years	Mean=8.2 (SD=NR) years Range=0.5–19 years	100.0	NR	Mean=9.6 (SD=NR) Range=5.9–12.9	Mean= 112.6 (SD=1.9)	NR	Unclear
Pramming et al.[89]	1986	Type 1	16	Median=28 years Range=20-46 years	Median=12 years Range 4-28 years	16	NR	8.7	NR	NR	Unclear
Herold et al.[91]	1985	Type 1	12	Mean=31.3 (SD=2.1) years Range=NR	Mean=10.1 (SD=2.4) years Range=NR	50.0	NR	Mean=10.8 (SD=0.9) Range=NR	NR	NR	Unclear
Holmes et al.[92]	1983	Type 1	12	NR	NR	50.0	NR	NR	NR	NR	Unclear

*Drivers with a history of a driving mishap
†Drivers with no history of a driving mishap
NA=Not applicable; NR=Not reported; SD=Standard deviation; SE=Standard error

4.2.5. Findings for Key Question 2

4.2.5.1. Simulated Driving Studies

The present 2010 update did not identify any additional studies that examined driving simulator performance relevant to this key question. The results that follow are unchanged from the 2006 report. The findings of the three included studies that assessed the effects of hypoglycemia on simulated driving are summarized in Table 28. All three studies found that driving ability was impaired during hypoglycemia across several variables. Despite agreement across studies that driving ability is impaired by hypoglycemia, there is little agreement as to which aspects of driving become impaired and at what level of hypoglycemia these impairments begin to become manifest.

Table 28: Hypoglycemia and Simulated Driving Ability

Reference	Year	Simulator Details	Measure of Performance	Change from Euglycemic Condition (BG Level 1)	Change from Euglycemic Condition (BG Level 2)	Change from Euglycemic Condition (BG Level 3)
Cox et al.[23, 77]	2000	Atari Research Driving Simulator (3-screen version). Set up to simulate 16 miles of a typical grade 2 U.S. highway.	Condition (BG range)	4.0–3.3 mmol/L	3.3–2.8 mmol/L	<2.8 mmol/L
			SD steering (z-score)	0.04 (P=NS)	−0.02 (P=NS)	−0.04 (P=NS)
			Off-road (z-score)	0.25 (P=NS)	0.45 (P=NS)	0.57 (P=NS)
			Risk midline (z-score)	0.05 (NS)	0.17 (NS)	0.11 (P <0.01)
			Low speed (z-score)	0.01 (P=NS)	−0.05 (P=NS)	0.37 (P=NS)
			High speed (z-score)	0.23 (P <0.01)	0.56 (P <0.001)	0.26 (NS)
			SD speed (z-score)	−0.09 (P=NS)	0.09 (P=NS)	0.23 (P=NS)
			Inappropriate braking (z-score)	0.00 (P=NS)	0.61 (P=NS)	0.00 (P=NS)
			Composite driving impairment score (z-score)	0.83 (P <0.01)	1,83 (P <0.005)	1.52 (P <0.005)
			Percent of patients significantly impaired	12	26	16
			Patient's impression of difficulty in driving (z-score)	0.30 (P <0.05)	0.35 (P <0.01)	0.54 (P <0.01)
			Percent of subjects who detected driving impairment (z-score)	21	22	25
			Percent of subjects who detected hypoglycemia (z-score)	15	33	79
			Number of subjects who took corrective action to treat hypoglycemia (z-score)	5	3	22
Cox et al.[82]	1993	Atari Research Driving Simulator (single-screen version: low resolution 513 by 384 pixels) Participants underwent 4 4-minute tests a day for 2 days	Condition	3.6+/-0.3 mmol/L	2.6+/-0.28 mmol/L	
			Steering			
			Swerving (z-score)	P=NS	P<0.03	
			Spinning (z-score)	P=NS	P<0.04	
			Time across midline (seconds)	P=NS	P<0.05	
			Time off road (seconds)	P=NS	P<0.01	
			Speed Control			
			Speeding (seconds >10% speed limit)	P=NS	P=NS	
			Driving too slow (seconds <30% below speed limit)	P=NS	P<0.04	
			Smooth braking	P=NS	P=NS	
				P=NS	P=NS	

Reference	Year	Simulator Details	Measure of Performance	Change from Euglycemic Condition (BG Level 1)	Change from Euglycemic Condition (BG Level 2)	Change from Euglycemic Condition (BG Level 3)
Hoffman et al.[87]	1989	M-8000A Driver Simulator System 3-video scenarios. Subject required to respond in simulator by adjusting speed and direction of simulated vehicle to avoid hazards. Errors automatically collected.	Condition *Signaling, Steering and Acceleration* Performance poorer for several (n not reported) individuals during hypoglycemia	3.1 mmol/L P=NS		

4.2.5.2. Cognitive and Psychomotor Function Studies

The findings of the 27 studies included in the present report that evaluated cognitive and/or psychomotor function in individuals with diabetes are summarized in Table 29. Because of the diversity in the cognitive and psychomotor function tests used, the varied testing conditions, and the variable blood glucose levels at which testing was performed, we have not attempted to pool the outcome data using meta-analysis. Instead we provide a qualitative summary of the available outcome data.

The results of the studies included in the table consistently demonstrate that moderate hypoglycemia has an acute deleterious effect on the ability of some individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks. At the present time no comparable data sets are available for individuals who do not require insulin to control their diabetes.

Cognitive/Psychomotor Abilities

While on average, cognitive and psychomotor performance among individuals with type 1 diabetes was significantly impaired during moderate hypoglycemia, some individuals appeared to be unaffected by low blood glucose levels. Aside from a very limited history of hypoglycemic episodes, the defining characteristics of this latter group of individuals remain unclear.

All studies presented in Table 28 revealed that hypoglycemia impairs a broad array of cognitive and/or psychomotor functions at varying levels of hypoglycemia, including attention, memory, visual and auditory perception, and spatial orientation, all of which are important for safe driving.

Spatial Abilities

The effect of hypoglycemia on spatial cognitive abilities has not been investigated in detail, even though it is a component of some tests used to assess other aspects of cognition. Spatial abilities are defined as the ability to generate, retain, retrieve and transform or manipulate structured visual images to orientate

and interpret the surrounding environment – critical components of day-to-day functioning. Only one recent study, Wright et al. (2009), examined spatial performance in-depth.

Wright et al. conducted nine tests, most of which were drawn from the French and Ekstrom Kit of Factor-Referenced Cognitive Tests. The authors found that acute, insulin-induced hypoglycemia causes significant decrements in most spatial cognitive abilities. This impairment of function was accompanied by deterioration in speed of mental processing as demonstrated by the decrement in score for the Digit Symbol Substitution Test. The effect sizes obtained indicate the development of medium to large decrements in spatial abilities during hypoglycemia in adults with type 1 diabetes.

Spatial abilities are relevant to the everyday activities of individuals with type 1 diabetes, and there are now data to show that part of the inability to manage complex tasks during hypoglycemia may be related to the inability to efficiently carry out spatial cognitive operations.

Sensory Information Processing

Several of the studies looked at visual and auditory processing outcomes during induced hypoglycemia in individuals with type 1 diabetes. Gold et al. (1995) found that rapid visual information processing (RVIP) tasks are impaired during hypoglycemia. Disruptions in visual processing tasks, such as RVIP, are of practical importance when considering impact on driving. Moreover, in the study by Gold, individuals with impaired hypoglycemia awareness demonstrated a delay in recovery of normal function even after normal blood glucose levels were restored (i.e., euglycemia). The authors cautioned that drivers or individuals who operate heavy machinery should be instructed not to resume work for a period of at least 30-45 minutes after restoration of blood glucose to normal levels. Similarly, Ewing et al. reported that visual inspection and visual change detection tasks are impaired in individuals with type 1 diabetes during moderate levels of hypoglycemia.

Strachan et al. (2003) found that moderate hypoglycemia in people with type 1 diabetes not only provoked higher cortical decrements, but also caused disruption of basic processing of auditory information. Acute hypoglycemia caused a significant disruption in auditory temporal processing and in a single aspect of “simple” auditory discrimination (the ability to distinguish the louder of two auditory tones) in adults with type 1 diabetes who had moderate to poor glycemic control. These data are consistent with the results of a previous Strachan study. Other aspects of “simple” auditory discrimination, namely the ability to discriminate tone duration and pitch, were not affected by hypoglycemia. This could indicate that these abilities have an innate resistance to the effects of neuroglycopenia, but could also be related to differences in the glycemic thresholds at which the performance of these tests becomes impaired.

Hypoglycemia Awareness

Several of the included studies examine the impact that hypoglycemia awareness has on cognitive and psychomotor deterioration during hypoglycemia, as well as its impact on recovery of performance as blood glucose levels are restored to normal. Individuals who demonstrate diminished or absent hypoglycemia awareness are those individuals who are either unaware that they are hypoglycemic or underestimated the impact that hypoglycemia has on their cognitive and psychomotor function. For example, Heller et al. noted that more than 70 percent of enrollees in their study were unaware that their

blood glucose levels were clamped at 2.5 mmol/L (moderate hypoglycemia), yet all of these individuals demonstrated impaired reaction times.

Several of the studies also examined judgments made by included patients regarding their ability to drive during induced hypoglycemia. For example, Weinger et al. noted that several individuals in their study with moderate symptomatic hypoglycemia (blood glucose level approximately 2.2 mmol/L) stated that, if allowed, they could drive safely at that time. Similarly, Cheyne et al. reported that seven of 24 individuals with type 1 diabetes indicated that they would drive during a state of induced hypoglycemia. Pramming et al. found that patients who recognized signs and symptoms of hypoglycemia only did so at low levels, between 1.5 and 2.1 mmol/L. Unexpectedly, for 12 of 16 patients, neuropsychological performance deteriorated at just below 3 mmol/L, but not one perceived he was in a state of hypoglycemia.

These findings have important safety implications.

Recovery from Hypoglycemia

A number of studies also examined cognitive and psychomotor performance following recovery of plasma glucose to normal values following induced hypoglycemia. In Fanelli et al. (2003), Zammitt et al. (2008) and Gold et al. (1995), the cognitive performance of their subjects was still impaired during recovery from hypoglycemia.

Fanelli et al., which compared cognitive impairment based on the slow and rapid fall in glucose levels, discovered that five out of seven tasks were still deteriorated in both groups after recovery from hypoglycemia. Gold et al. found that insulin-dependent diabetics with impaired hypoglycemia awareness exhibited more profound cognitive dysfunction during blood glucose recovery, and this impairment continued far longer than in those who had normal awareness.

Although Zammitt et al. found that insulin-dependent diabetics with impaired awareness suffered from cognitive dysfunction in recovery as well, Zammitt's results differed from Gold's in that the subjects with unimpaired awareness of hypoglycemia tended to suffer cognitive dysfunction for 35 minutes longer than those with impaired awareness. Zammitt also observed that cognitive performance in the impaired awareness group did not deteriorate significantly during hypoglycemia.

Individual Difference in the Impact of Hypoglycemia on Cognitive and Psychomotor Performance

The Gonder-Frederick et al. study sought to evaluate the individual differences in performance under mild and moderate states of induced hypoglycemia. One of the interesting findings of this study was that even very mild hypoglycemia (3.6 mmol/L) can adversely affect cognitive and motor performance in some adults with IDDM. However, an equally important finding was that the degree to which individuals were impacted varied. During mild hypoglycemia, 19 percent of the subjects exhibited clinically significant performance deterioration, while almost half showed little or no deterioration. When glucose levels were lowered further, performance generally deteriorated even more, but again response varied across individuals. At 2.6 mmol/L, clinically significant deterioration occurred in more than 50 percent of the subjects, but 15 percent showed little or no performance disruption. Moreover, the strong relationship between individual performance deterioration at original and repeat testing indicates that individual differences in reaction to hypoglycemia are not random but rather stable across time.

Table 29: Hypoglycemia and Cognitive and/or Psychomotor Function

<table>
<tr><th>Reference</th><th>Year</th><th>Findings</th><th>Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive</th></tr>
<tr><td>Wright et al.[70]</td><td>2009</td><td><u>Effects of Acute Insulin-Induced Hypoglycemia on Spatial Abilities in Adults With Uncomplicated Type 1 Diabetes</u>
<u>Symptom Scores</u>
Significant increments occurred in total autonomic (P<0.001), total neuroglycopenic (P<0.001), and malaise symptom scores (<0.001) during hypoglycemia.
<u>Digit Symbol Substitution Test (DSST)</u>
Scores were significantly lower during the hypoglycemia study period (72.4±20.2) compared with those during euglycemia (84.6±20.7) (P<0.001), confirming that a standard measure of speed of information processing was significantly impaired at blood glucose concentrations of 2.5 mmol/L.
<u>Trail Making B Test (TMB)</u>
No statistical differences between hypoglycemia (score of 50.4±20.9 s) and euglycemia (score of 38.9± 11.5 s) (P =0.07).
<u>Spatial Ability</u>
Hypoglycemia resulted in a significantly lower score on all of the spatial ability tests except the map memory test. Cohen's d results have shown that the impact of hypoglycemia on these spatial abilities was medium to large. Moreover, the ηp² values indicate that the hypoglycemia condition accounted for a large proportion of the variance in the results. No significant effects were observed of order of exposure to glycemic condition or test battery.
<table>
<tr><th>Spatial Test</th><th>Euglycemia Score</th><th>Hypoglycemia Score</th><th>P</th><th>Cohen's d</th><th>ηp²</th></tr>
<tr><td>Hidden pattern</td><td>94.5±21.8</td><td>73.7±21.0</td><td><0.001</td><td>0.97</td><td>0.627</td></tr>
<tr><td>Card rotations</td><td>51.9±15.5</td><td>40.4±18.7</td><td>0.001</td><td>0.67</td><td>0.580</td></tr>
<tr><td>Cube comparison</td><td>11.7±4.1</td><td>9.4±5.7</td><td>0.03</td><td>0.46</td><td>0.28</td></tr>
<tr><td>Paper folding</td><td>6.0±0.9</td><td>4.7±2.0</td><td>0.001</td><td>0.61</td><td>0.604</td></tr>
<tr><td>Map memory</td><td>8.6±3.1</td><td>7.8±2.1</td><td>0.3</td><td>0.30</td><td>0.081</td></tr>
<tr><td>Maze tracing</td><td>11.1±3.0</td><td>9.4±2.5</td><td><0.001</td><td>0.62</td><td>0.621</td></tr>
</table></td><td>NR</td></tr>
<tr><td>Geddes et al.[71]</td><td>2008</td><td><u>Effects of Acute Insulin-induced Hypoglycemia on Psychomotor Function in People with Type 1 Diabetes and Non-Diabetic Controls</u>
<u>Four-Choice Reaction Times</u>
Acute hypoglycemia caused a significant increase in mean four-choice reaction times, both in the type 1 diabetes (P=0.02, η2=0.34) and non-diabetic (P=0.008, η2=0.36) groups. There was no difference between groups (p=0.76).
<u>Hand Dexterity</u>
In the test of hand dexterity, no significant differences were observed in the type 1 diabetes group between euglycemia and hypoglycemia (P=0.44, η2=0.045), but test time significantly increased in the non-diabetic group (P=0.004, η2=0.37). There was no difference between groups (P=0.38).
<u>Hand Steadiness Test</u>
In the hand steadiness test, no decrease was seen in the diabetic group (P=0.11, η2=0.18) during hypoglycemia, but a significant decrement was seen during hypoglycemia (P=0.003, η2=0.40) in the non-diabetic group. Effects of hypoglycemia differed significantly between groups (P=0.021).
<u>Tracing Time</u>
No significant change in tracing time was observed in either group [non-diabetic group (P=0.480, η2=0.030); type 1 diabetes group (P=0.39, η2=0.06)]. No group differences were seen (P=0.70).
<u>Time on Target</u>
Scores for time on target were significantly greater during euglycemia than during hypoglycemia in the type 1 diabetes group (P=0.04, η2=0.27) and the non-diabetic group</td><td>NR</td></tr>
</table>

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		(P=0.018, η2=0.29). No group differences were observed (P=0.59). *Total Body Sway* No significant change in total body sway was observed in the group with type 1 diabetes (P=0.34, η2=0.08). In the non-diabetic group, total body sway increased during hypoglycemia (P=0.004, η2=0.41). Group differences were observed (P=0.042). *Grip Strength* No significant deterioration of grip strength was observed during hypoglycemia compared with euglycemia in either group (non-diabetic group: P=0.90, η2=0.001; type 1 diabetes: P=0.96, η2=0.000). No group differences were found (P=0.90).	
Zammitt et al.[72]	2008	Delayed Recovery of Cognitive Function Following Hypoglycemia in Adults With Type 1 Diabetes Effect of Impaired Awareness of Hypoglycemia Poorer performance during hypoglycemia versus euglycemia was seen for all cognitive tasks. However, cognitive performance was significantly impaired in normal hypoglycemia awareness (NHA) subjects alone, whereas only nonsignificant trends were seen in impaired hypoglycemia awareness (IHA) subjects. Compared with NHA subjects, IHA patients demonstrated smaller deterioration in performance and more rapid recovery following hypoglycemia. *Digit Symbol Substitution Test* • NHA: Significantly reduced performance during hypoglycemia. • IHA: Not significantly impaired during hypoglycemia except after 60 minutes. • Interaction between glycemic condition and hypoglycemic awareness was significant only at the start of hypoglycemia (P=0.009).This suggests that hypoglycemia caused significantly greater impairment in NHA subjects than in IHA subjects. • There was no persistence of impairment of DSST performance after euglycemia was restored. *Trail Making B Test* • NHA: Performance deteriorated significantly during hypoglycemia but reverted to baseline as soon as euglycemia was restored. • IHA: Not significantly impaired during hypoglycemia. • The glycemia-awareness interaction was not significant at any point in time. • There was no persistence of impairment of performance after euglycemia was restored. *Choice Reaction Time* Performance was impaired during hypoglycemia and at 20, 30 and 40 minutes after euglycemia was restored (P=0.04, η^2=0.125). Glycemia-awareness interaction was significant only at the end of hypoglycemia (P=0.045,η^2=0.124). This implies that the NHA group, relative to their baseline performance, was more affected during hypoglycemia than the IHA group but there were no significant between-group differences during recovery.	NR
McAulay et al.[73]	2006	Attentional Functioning During Acute Hypoglycemia in People with Type 1 Diabetes *Tests of Everyday Attention* Visual Selective Attention The mean number of map symbols circled was lower during hypoglycemia. However, in the telephone search task, no difference was shown between euglycemia and hypoglycemia in the number of symbols located. The mean time taken to complete the task, however, increased significantly during hypoglycemia. Auditory Selective Attention/Auditory Verbal Working Memory There was a large decline during hypoglycemia with the elevator test, as there was with the elevator test reversal. Sustained Attention There was no deterioration during hypoglycemia using either the lottery ticket or elevator counting tests. Attentional Switching No difference was observed in the raw score between the two conditions, but a significantly longer time was required to complete the task during hypoglycemia.	NR

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		Divided Attention No significant difference in the number of symbols located during either study condition. However, the time taken to complete the task was higher during hypoglycemia. *Raven's Standard Progressive Matrices* No significant differences were observed between euglycemia and hypoglycemia in either the scores achieved or the time taken to complete the test.	
Cheyne et al.[74]	2004	Influence of Alcohol on Cognitive Performance During Mild Hypoglycemia; Implications for Type 1 Diabetes *Four-Choice Reaction Time* Both hypoglycemia (with placebo) and alcohol were associated with deterioration in four-choice reaction time; this effect was additive. During hypoglycemia, reaction time slowed by +38.5 ms (4.5, 73), P=0.038. Ingestion of alcohol was also associated with a similar slowing of reaction time during euglycemia, +35.0 ms (20, 50), P=0.0003. The combination of alcohol and hypoglycemia caused reaction time to slow by 73.5 ms [35, 112) P=0.0016. *Trail Making B* Alcohol ingestion was associated with deterioration in trail making [+14.2 s (5.1, 23.4), P=0.007], whereas hypoglycemia alone did not affect it. When alcohol and hypoglycemia were combined, the time taken to complete the task was slowed [+19 s (6.3, 31.7), P=0.009). *Digit Symbol Substitution* The combination of hypoglycemia and alcohol resulted in a deterioration in score of -3.5 (-6.2,-0.7), P=0.021, on the digit symbol task. *Visual Change Detection* The combination of hypoglycemia and alcohol resulted in a deterioration in score of -2.6 (-4.3, -0.9), P=0.008 during the visual change detection test. *Hazard Perception* Hazard perception was unaffected by alcohol, hypoglycemia or a combination of both. *Symptoms* Neuroglycopenic symptom scores increased after ingestion of alcohol [+19 {4, 14), P=0.03] and during hypoglycemia 1+15 (2, 28), P=0.04]. When hypoglycemia and alcohol were combined, subjects were more symptomatic (+35 (11, 59), P=0.01]. Autonomic symptoms also increased during hypoglycemia [+17 (5, 29), P=0.01], but not after alcohol alone. When hypoglycemia and alcohol were combined there was an increase in score of +12 (2, 22), P=0.02.	*Awareness* Eight of 17 subjects correctly identified their hypoglycemic state during hypoglycemia. Six of 17 subjects correctly identified their hypoglycemic state during hypoglycemia + alcohol. *Driving* When asked if driving would be impaired, scores increased from 7 to 24 during hypoglycemia alone to 50 after alcohol alone (maximum score 100). When hypoglycemia was combined with alcohol there was no significant increase in score (53) compared with alcohol on its own (P=0.66). When asked how likely they would be to drive during test battery 2, average score did not change significantly during hypoglycemia with placebo (f - 0.44). However, subjects were less likely to drive after alcohol (P=0.01). When hypoglycemia was combined with alcohol there was no significant change in score.
Fanelli et al.[75]	2003	Clinical Symptoms and Cognitive Function to Hypoglycemia in Type I Diabetes (Fast Fall and Slow Fall) *Cognitive Tests For Fast-Fall and Slow-Fall Blood Glucose Levels* • All cognitive tests deteriorated during hypoglycemia both after fast-fall of blood glucose	NR

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		and slow-fall of blood glucose, with the exception of the digit vigilance test, which deteriorated only after the fast-fall and marginally after the slow-fall study (P=0.06). • In all hypoglycemia-mediated cognitive tests, deterioration was greater in the fast-fall than after the slow-fall study. Significant differences were, however, only seen for Trail Making B, Paced Auditory Serial Addition Task (PASAT), digit vigilance and verbal memory tests. *Recovery following Hypoglycemia* • After recovery from hypoglycemia, all cognitive tests remained deteriorated compared with the baseline, with the exception of digit span backward and digit vigilance, without differences between the fast- and slow-fall studies. • The protracted deterioration of the Trail Making A and B tests after recovery from hypoglycemia was best predicted by the duration of diabetes; the responses of PASAT tests were best predicted by pancreatic polypeptide concentrations; and the verbal memory test was best predicted by the percentage of HbA1c.	
Sommerfield et al.[6]	2003	Memory During Hypoglycemia in Individuals with Type 1 Diabetes *Verbal Memory* Acute hypoglycemia caused a significant deterioration in immediate verbal memory. *Immediate Visual Memory* Scores for both the Delayed AVLT and the Delayed Logical Memory Test were significantly worse during hypoglycemia. *Delayed Visual Memory* A significant decrement was observed. *Working Memory* All patients demonstrated a significant decrement during hypoglycemia. *Digit Symbol Test* The mean score of this test declined from 73.5 (11.2) during euglycemia to 62.9 (16.9) during hypoglycemia. *Trail Making B Test* The time taken to complete this test increased considerably from a mean 33.7 s (7.7) during euglycemia to 54.0 s (10.7) during hypoglycemia.	NR
Strachan et al.[76]	2003	*Digit Symbol and Trail Making B Tests* Hypoglycemia caused deterioration in mental efficiency. *Auditory Processing Test* Acute hypoglycemia caused deterioration in one of three measures of simple auditory processing, namely single-tone loudness. It also had a deteriorating effect in auditory temporal processing. The amplitude and latency of auditory N100, P200 and P300 event related potentials were not affected. However, the amplitude of the N240 potential was reduced during acute hypoglycemia.	NR
Lobmann et al.[78]	2000	Impairment and Recovery of Elementary Cognitive Function Induced by Hypoglycemia In Type 1 Diabetic Patients and Healthy Controls *Test of Selective Attention (custom test)* Selective attention diminished as a function of increased hypoglycemia. Response times increased significantly during hypoglycemia (P= 0.006] and decreased significantly with restoration of euglycemia (P <0.001).	NR
Weinger et al.[24]	1999	The Perception of Safe Driving Ability During Hypoglycemia in Patients with Type 1 Diabetes Mellitus *Trail Making Test Part B* Significant deterioration in test performance as a function of increasing hypoglycemia (P <0.001) *Choice Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia	• 22% considered themselves safe to drive when blood glucose level was ≤2.2 mmol/L (severe hypoglycemia).

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		(P <0.01) *Digital Vigilance Test* Significant deterioration in test performance as a function of increasing hypoglycemia (items scanned, P <0.001; omission errors, P <0.01) *Subtraction Test* Significant deterioration in test performance as a function of increasing hypoglycemia as measured by time (P <0.001) but not score (P=NS)	None of these individuals demonstrated serious cognitive impairment at these blood glucose levels. • 12% of individuals with severe hypoglycemia stated that they could drive safely • 12% of individuals demonstrated hypoglycemia unawareness.
Ewing et al.[8]	1998	Effect of Acute Hypoglycemia on Visual Information Processing in Type 1 Diabetes Mellitus *Cognitive Tasks: Digit Symbol Substitution Test and Trail Making B* During hypoglycemia, digit symbol task scores were reduced significantly [F(1,13)=26.8, p<0.001] and Trail Making B test completion times were prolonged significantly [F(1,13)=7.91, p<0.05, indicating general cognitive dysfunction. *Visual Acuity and Contrast Sensitivity* Hypoglycemia did not significantly affect visual acuity measurements. Contrast sensitivity deteriorated during hypoglycemia, although this did not achieve the conventional level of statistical significance [F(1,13)=4.14, p=0.06]. *Visual Inspection and Visual Change Detection* Inspection times increased from 44.2 (SD=5.3) ms during euglycemia to 56.5 (SD=14.5) ms during hypoglycemia [p<0.005]. Visual change detection scores decreased from 31.9 (SD=4.7) during euglycemia to 28.8 (SD=5.2) during hypoglycemia [p=0.006]. *Visual Movement Detection* The ability to detect visual movement was not altered significantly [P=0.176].	NR
Draelos et al.[79]	1995	Cognitive Function in Patients with Insulin-Dependent Diabetes Mellitus During Hyperglycemia and Hypoglycemia *Cognitive Function* • Deterioration in cognitive test scores at 2.2 mmol/L was significant for all tests (Visual Reaction Time, Trail Making Test Part B, Word Recall Task, Digit Sequence Learning Test, Verbal Fluency Test p<0.0001; Digit Vigilance Test, p<0.01). • The digit sequence learning and trail making tests showed the most profound deterioration at 2.2 mmol/L (19.9[SD=0.7] to 12.6[SD=1.4], and 63.1[SD=1.6] to 44.6[SD=2.7] respectively), while digit vigilance (% errors) and verbal fluency showed the least deterioration. • No association was found between cognitive function at any glucose level and long-term glycemic control (historic HbAlc) or more recent glycemic control (study HbAlc). • At 2.2 mmol/L there was no relationship between cognitive function and verbal IQ, suggesting that patients with higher verbal IQs may have had a greater deterioration in cognitive function during hypoglycemia. • Neither age, duration of diabetes, insulin level, nor counter-regulatory hormone concentration was correlated with cognitive function at any glucose level. *Gender Analyses* Women exhibited less of a performance decrement than men, from baseline (glucose = 8.9 mmol/L) to hypoglycemia (glucose = 2.2 mmol/L) on the trail making test (P=0.02) and on the percentage errors component of the digit vigilance test (P=0.03). Furthermore, these differences remained after controlling for glycemic control, duration of diabetes, and verbal	NR

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		IQ.	
Driesen et al.[80]	1995	Reaction Time Impairment in Insulin-Dependent Diabetes: Task Complexity, Blood Glucose Levels, and Individual Differences *Reaction Time (Simple)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.68, P <0.05) *Reaction Time (Choice Side)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.59, P <0.05) *Reaction Time (Choice Direction)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.55, P <0.05) *Reaction Time (Complex Side)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.58, P <0.05) *Reaction Time (Complex Direction)* Significant deterioration in test performance during moderate hypoglycemia (Cohen' s d= -0.44, P <0.05)	NR
Gold et al.[81]	1995	Hypoglycemia-Induced Cognitive Dysfunction in Diabetes Mellitus: Effect of Hypoglycemia Unawareness Overall performance in the combined group deteriorated during hypoglycemia in all tests. *Trail Making B* During TMB test, participants with impaired awareness were more impaired following recovery from hypoglycemia than the patients with normal awareness of hypoglycemia (P=0.04). *Paced Auditory Serial Addition Test* Hypoglycemia significantly deteriorated performance in PASAT tests in both groups, followed by recovery in performance after restoration of euglycemia (P<0.001). No group differences were observed. *Digit Symbol Substitution Test* DSST test scores was significantly affected by hypoglycemia in both groups, with a recovery in performance following restoration of euglycemia (P=0.03). No group differences were observed. *Rapid Visual Information Processing (RVIP)* Hypoglycemia significantly affected performance in RVIP tests in both groups (P=0.004). On recovery from hypoglycemia, the scores in the patients with normal awareness returned to the baseline score, whereas those patients with impaired awareness of hypoglycemia remained significantly impaired (P=0.02).	NR
Gonder-Frederick et al.[11]	1994	Individual differences in neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM *Mild vs. Moderate Hypoglycemia* • Mild hypoglycemia (3.6 mmol/L) resulted in significant deterioration on every test with the exception of Trail Making B. • Moderate hypoglycemia (2.6 mmol/L) resulted in significant deterioration on every test with the exception of coin-flipping (difficult). Performance deterioration scores were significantly greater at moderate hypoglycemia compared with mild hypoglycemia (P<0.001). *Impact of Previous Severe Hypoglycemia* Subjects with a history of hypoglycemic unconsciousness (n=8) had significantly higher deterioration scores than subjects with no such history (mild hypoglycemia, P=0.05; moderate hypoglycemia, P=0.01). *Gender Analyses*	NR

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		During mild hypoglycemia, performance deteriorated significantly more in men than in women (P=0.04). No gender difference was observed at moderate hypoglycemia (P=0.27).	
Cox et al.[83]	1993	Disruptive Effects of Acute Hypoglycemia on Speed of Cognitive and Motor Performance Only the cognitive tasks (e.g., Paced Auditory Serial Addition Test [PASAT]) were disrupted and only during hypoglycemia (mean = 2.6 mmol/L, PASAT 1 subjects versus control subjects P < 0.04, PASAT 2 subjects versus control subjects P < 0.03). Performance decay was significantly related to baseline performance for PASAT 1 (r=0.59), PASAT 2 (r=0.69), and FTT 1 (r=0.65); performance decay was also related to absolute blood glucose level at nadir for PASAT 1 (r=0.72) and PASAT 2 (r=0.61).	NR
Blackman et al.[84]	1992	Hypoglycemic thresholds for cognitive dysfunction in IDDM *Reaction Time* Reaction time increased significantly (P <0.001) during hypoglycemia (2.5 mmol/L).	21.4% of enrollees reported that they did not experience symptoms of hypoglycemia when blood glucose levels clamped at 2.5 mmol/L. Whether these three individuals demonstrated slowed reaction times was not reported.
Lingenfelser et al.[85]	1992	Cognitive and Psychomotor Function During Severe Insulin-Induced Hypoglycemia in Insulin-Dependent Diabetic Patients *Digit Symbol Test* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.05). *Digit Connection Test* No significant change in performance observed. *Aiming Center I* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Aiming Center II* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Line Tracing Time* No significant change in performance observed. *Line Tracing Errors* Significant deterioration in test performance as a function of increasing hypoglycemia observed (*P* <0.01). *Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia observed *(P* <0.01).	40% of enrollees were unaware of the fact that they were hypoglycemic (blood glucose level clamped at 2.2 mmol/L).
Widom et al.[86]	1990	Glycemic Control and Neuropsychologic Function During Hypoglycemia in Patients with Insulin-Dependent Diabetes Mellitus *Cognitive Function Tests* • Dysfunction in visual-motor skills, visual-spatial skills, or global cognitive skills (e.g., perceptual speed test, trail making test, and symbol digit modalities test, occurred during hypoglycemia for all groups. • Patients with well controlled diabetes did not differ statistically from those with poorly controlled diabetes regarding the median glucose threshold for dysfunction in visual-spatial skills, visual motor skills, or global cognition. *Thresholds for Counterregulatory Hormone Release*	NR

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
		Glycemic thresholds for an increase in adrenergic symptoms and release of epinephrine, norepinephrine, cortisol, and growth hormone were lower in patients with well controlled diabetes that in those with poorly controlled diabetes (P<0.05 to 0.005).	
Hoffman et al.[87]	1989	Changes in Cortical Functioning with Acute Hypoglycemia and Hyperglycemia in Type I Diabetes *Reaction Time* Reaction time slower during hypoglycemia. However, considerable variation was seen and overall effect failed to reach significance (P=0.126). *Trail Making Test Part A and B* Significant reduction in Trail Making t B (but not A) in performance during hypoglycemia (P=0.002). *Pursuit Rotor Performance* Significant reduction in pursuit-rotor performance during hypoglycemia (P=0.007).	NR
Heller et al.[88]	1987	Influence of Sympathetic Nervous System on Hypoglycemic Warning Symptoms *Reaction Time* Significant deterioration in test performance as a function of increasing hypoglycemia observed *(*P <0.01).	73.3% of enrollees unaware of hypoglycemia (blood glucose clamped at <2.5 mmol/L). All individuals demonstrated prolonged reaction times.
Holmes et al.[90]	1986	Simple Versus Complex Performance Impairments at Three Blood Glucose Levels *Simple Reaction Time* No significant effect *Go/No-Go Reaction Time* Significant reduction in performance during hypoglycemia (P<0.05) *Choice Reaction Time* Significant reduction in performance during hypoglycemia (P<0.05)	NR
Pramming et al.[89]	1986	Cognitive Function During Hypoglycemia in Type 1 Diabetes Mellitus Lowering the blood glucose concentration to below 2 mmol/L was accompanied by cognitive dysfunction in all patients. Neuropsychological performance deteriorated at a blood glucose concentration just below 3 mmol/L in 12 of 16 patients, though none perceived this state as hypoglycemia. The outcome of tests such as trail making and subtraction suggest that the performance of everyday tasks that entail planning and control, will suffer even at a subnormal blood glucose concentration of around 3 mmol/L, which is not usually considered to be hypoglycemic. It was found that much prompting and encouragement were needed at low blood glucose concentrations (hypoglycemia) compared with euglycemic periods. The patients were often well aware of the character of the test and the performance required, but their executive functions were negatively affected.	Four of 16 patients (25%) were unaware of hypoglycemia at 2 mmol/L nadir.
Herold et al.[91]	1985	Variable Deterioration in Cortical Function During Insulin-Induced Hypoglycemia *Reaction Time* Mean reaction time increased significantly during hypoglycemia when compared with euglycemic state (P<0.02). The range of individual responses was wide. Five of 12 individuals did not demonstrate increases in reaction time.	16.6% of enrollees unaware of hypoglycemia (blood glucose levels clamped at approx. 2.4 mmol/L). Both individuals demonstrated prolonged reaction times.

Reference	Year	Findings	Percent Who Did Not Perceive Onset of Symptomatic Hypoglycemia or Believed that They Were Safe to Drive
Holmes et al.[92]	1983	Cognitive Functioning at Different Glucose Levels in Diabetic Persons *Digit supraspan* No significant effect *Rey auditory verbal learning test* No significant effect *Matching Familiar Figures Test (MFFT)* No significant effect *Delayed reaction time* Significant reduction in performance during hypoglycemia (P <0.05) *Benton Visual Retention Task (BVRT)* No significant effect *Nelson Denny Reading Test (NDRT)* No significant effect *Mathematical computations* Significant reduction in performance during hypoglycemia (P <0.05)	NR

4.2.6. Section Summary

The conclusions of our assessment of the evidence addressing Key Question 2 are presented below. Note that none of the included studies examined the effects of hypoglycemia on simulated driving ability, or on cognitive or psychomotor function in a group of CMV drivers with diabetes. Also note that all of the included studies examined the effects of hypoglycemia in individuals with type 1 diabetes. No individuals with type 2 diabetes were enrolled in any included study. Even if current interstate restrictions on CMV drivers with insulin-treated diabetes are lifted, non-insulin-treated individuals with type 2 diabetes will still make up the vast majority of CMV operators who have the disorder. Consequently, the degree to which the findings of the included studies, particularly findings related to specific driving skills, can be generalized to CMV operators is unclear.

3. **Hypoglycemia has a significant deleterious effect on the driving ability of some individuals with type 1 diabetes (or IDDM) when measured using a driving simulator (strength of evidence: moderate).**
   - **Due to a paucity of data (only two studies), no attempt was made to determine a quantitative estimate of the relationship between the deterioration in driving competency and blood glucose levels.**

Three small (total N=80), moderate-quality studies assessed the effects of induced hypoglycemia on simulated driving ability. All three studies found that driving ability was impaired during hypoglycemia across several variables. Despite agreement across studies that driving ability is impaired by hypoglycemia, there is little agreement as to exactly which aspects of driving ability are most vulnerable to hypoglycemia, and at what levels of hypoglycemia these impairments begin to become manifest.

4. **Hypoglycemia has a significant deleterious effect on the cognitive and psychomotor function of individuals with type 1 diabetes (or IDDM) as measured by a number of different tests of cognitive function (strength of evidence: moderate).**

- **Because of the variety of cognitive and psychomotor function tests used, the variable testing conditions, and the variable blood glucose levels at which testing was performed, no attempt was made to determine a quantitative estimate of the relationship between functional loss and blood glucose levels.**

Twenty-four small, low- to moderate-quality studies assessed the effects of insulin-induced hypoglycemia on cognitive and psychomotor function. These 24 studies consistently demonstrated that moderate hypoglycemia had an acute deleterious effect on the ability of some (but not all) individuals with insulin-dependent diabetes to perform a wide variety of cognitive and psychomotor tasks. At the present time, no comparable data sets are available for individuals who do not require insulin to control their diabetes.

The 24 included studies consistently demonstrate that moderate hypoglycemia (blood glucose levels in the region of 2.5-3.0 mmol/L[45–54 mg/dl]) has a deleterious acute effect on the ability of some individuals with type 1 diabetes to perform a wide variety of cognitive and psychomotor tasks. While on average, cognitive and psychomotor performance was significantly impaired during moderate hypoglycemia, some individuals appeared not to be affected by these levels of hypoglycemia. Other individuals appeared to be unaware that they were hypoglycemic and/or they tended to underestimate the impact that hypoglycemia was having on their cognitive and psychomotor function. For example, Weinger et al. noted that 12 percent of the individuals in their study demonstrated hypoglycemia unawareness and several individuals with severe hypoglycemia stated that, if allowed, they could drive safely. Heller et al. noted that over 70 percent of enrollees in their study were unaware that their blood glucose levels were clamped at 2.5 mmol/L (moderate hypoglycemia), yet all of these individuals demonstrated impaired reaction times.

4.3. Key Question 3: What risk factors are associated with an increased incidence of severe hypoglycemia, and what is the incidence of severe hypoglycemia with different treatments and treatment modalities?

The primary aim of modern treatments for individuals with diabetes is to control blood glucose levels at near normal levels. This is because studies have shown that maintaining tight control reduces the risk for developing the long-term complications associated with type 1 and type 2 diabetes (e.g., retinopathy, nephropathy, neuropathy, cardiovascular disease, etc.).[1-4] For example, in a 2010 meta-analysis including seven trials and over 34,000 patients with type 2 diabetes, Zhang et al. demonstrated that intensive glucose control significantly reduced major cardiovascular events by 10 percent (RR=0.90, 95% CI 0.85–0.96; P=0.0006), and non-fatal myocardial infarction by 16 percent (0.84, 95% CI 0.76–0.93; P=0.0006). However, Zhang et al. also demonstrated that intensive glucose control resulted in significantly increased incidence of severe hypoglycemia (RR=2.30, 95% CI 1.74–3.03; P=0.00001).

The primary limiting factor for attaining tight control of blood glucose levels is hypoglycemia. Consequently, much effort has been exerted in the development of new drugs (e.g., meglitinides, thiazolidinediones, etc.), treatment regimes (e.g., combinations of long-acting and short-acting insulin), and treatment delivery methods (e.g., insulin pumps) that allow tight control while minimizing the risk for hypoglycemia.

This section of the evidence report is divided into three primary subsections.

4. In the first subsection, we provide a high-level summary of studies that have attempted to determine which treatment-related factors are associated with an increased risk for severe hypoglycemia. The purpose of this subsection is to highlight behavioral, demographic, and treatment-related risk factors that have been identified in the literature as contributing to an increased risk of hypoglycemia.
5. The second subsection provides a high-level summary of available systematic evidence reviews and meta-analyses that provide data on the incidence of severe hypoglycemia associated with specific treatment options. The purpose of this subsection is to determine whether there is any evidence that some treatment options, treatment regimes, or treatment delivery methods present less of a risk for the development of severe hypoglycemia than others. The treatment options considered are limited to those identified in the Background section of this evidence report and include only treatments that have FDA approval for marketing. We do not consider treatment options that are currently considered experimental or those that are no longer available (for instance, inhaled insulin).
6. The third subsection provides a high-level summary of risks associated with new injectable non-insulin based medications currently used to treat diabetes, including exenatide (Byetta®) and liraglutide (Victoza®).

4.3.1. Risk Factors for Hypoglycemia

The most appropriate study designs for the evaluation of risk factors associated with a particular condition among representative populations while controlling for other known risk factors come from epidemiology. A number of investigators have attempted to identify risk factors for severe hypoglycemia among individuals with diabetes. Findings from these studies are presented in Table 30. Figure 12 shows the behavioral, demographic, and treatment-related risk factors that are consistently identified as being associated with an increased incidence of hypoglycemia.

Table 30: Significant Risk Factors for Severe Hypoglycemia

Reference	Year	N=	Diabetes Type	Study Details	Definitions Used	Risk Factors Identified
Davis et al.[93]	2010	616	Type 2	Prospective longitudinal observational cohort study (8-year follow-up)	Severe hypoglycemia = requiring ambulance attendance, emergency department services, and/or hospitalization	*Severe hypoglycemia* • Insulin treatment • Duration of insulin treatment • Estimated glomerular filtration rate less than 60 ml/min per 1.73 m(2) • Peripheral neuropathy • Education beyond primary level • Past severe hypoglycemia • HbA1c
Akram et al.[94]	2006	2,833	Type 2	Systematic review: 11 studies • 5 retrospective (n=1,122) • 6 prospective (n=1,711)	Severe hypoglycemia = varied between studies but generally included severe symptoms affecting mentation or requiring the assistance of others	*Severe hypoglycemia* • Impaired hypoglycemia awareness • Older age • Longer duration of diabetes • Longer duration of insulin therapy
Akram et al.[95]	2005	401	Type 2	Survey (retrospective) Single center: UK and Denmark (4 centers) Primary outcome = severe hypoglycemic events occurring in previous year (self-reported)	Severe hypoglycemia = the need for assistance from another person to treat the condition in the preceding year	*Severe hypoglycemia* • Longer duration of insulin therapy (10 years) • Impaired hypoglycemia awareness • Multiple (four times) daily injections • Marital status (being married)
Murata et al.[96]	2005	344	Type 2	Prospective cohort study (1 year) Primary endpoint = clear relationship between a factor and occurrence of a mild or severe hypoglycemic event in previous year (self-reported)	Mild hypoglycemia = mild to moderate symptoms including palpitations, diaphoresis, weakness or anxiety. Severe hypoglycemia = severe symptoms affecting mentation or requiring the assistance of others.	*Mild hypoglycemia* • Recent increase in medication dose • Excessive dieting or weight loss • Missed meal • Wrong medication dose • Concurrent illness • Exercise *Severe hypoglycemia* • Excessive dieting or weight loss • Missed meal • Wrong medication dose
Donnelly et al.[97]	2005	267	Type 1 and type 2	Prospective Ordinal logistic regression was performed to identify potential predictors of hypoglycemia. Primary outcome = moderate or severe hypoglycemic events occurring during 1 month (self-reported)	Mild hypoglycemia = mild to moderate symptoms requiring remedial action. Severe hypoglycemia = severe symptoms affecting mentation or requiring the assistance of others.	*Moderate or severe hypoglycemia* • Type of diabetes (type 1 higher risk) *Type 1 diabetes* • Event in previous month • Concurrent use of any other drug • Insulin dose *Type 2[†]: diabetes* • Event in previous month

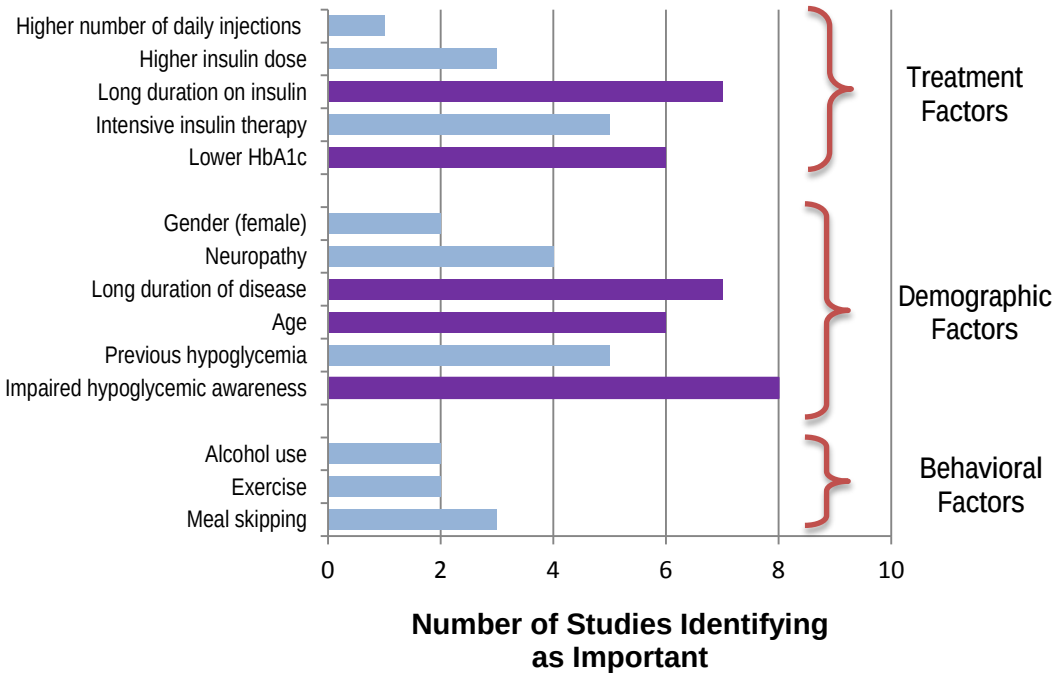
Reference	Year	N=	Diabetes Type	Study Details	Definitions Used	Risk Factors Identified
						• Duration of insulin use
Pederson-Bjergaard et al.[98]	2004	1,076	Type 1	Survey (retrospective) Multicenter: UK and Denmark (4 centers) Primary outcome = severe hypoglycemic events occurring in previous year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	*Univariate factors* • Age • Duration of diabetes • Female sex • HbA1c • Presence of diabetic neuropathy • Impaired hypoglycemic awareness • Absent hypoglycemic awareness • Single or divorced • Use of alcohol • Smoking *Multivariate factors* • Reduced hypoglycemia awareness; • Symptomatic peripheral neuropathy; • Smoking
Henderson et al;[71]	2003	215	Type 2	Retrospective Survey of insulin-treated type 2 diabetics	Mild hypoglycemia = self-treated Severe hypoglycemia = required assistance	*Risk factors:* • Impaired awareness • Increasing duration of disease • Increasing duration of insulin therapy
Leese et al[99]	2003	8,655	Type 1 and type 2	Retrospective Hospital records; routinely collected datasets were analyzed in a population of 367,051 people, including 8,655 people with diabetes. Data collected for a 1-year period.	Severe hypoglycemia = required emergency assistance from Ninewells Hospital and Medical School personnel including those in primary care, ambulance services, hospital accident and emergency departments, and inpatient care	*Severe hypoglycemia (type 1 and type 2)* • Age • Disease duration • Socioeconomic status
Allen et al.[100]	2001	415	Type 1	Prospective study Demographic and self-management measures taken All patients had history of diabetes >4.5 years Frequency and severity of hypoglycemia self-reported		*Frequency of hypoglycemia (univariate)* • Low HbA1c • Intensive insulin therapy • Frequency of blood glucose measurement in a day • Age • White race • Mother's education *Frequency of severe hypoglycemia (univariate)* • Low HbA1c • Frequency of blood glucose measurement in a day • Age • Female sex • Medicaid vs. other

Reference	Year	N=	Diabetes Type	Study Details	Definitions Used	Risk Factors Identified
						Frequency of hypoglycemia (multivariate) • Low HbA1c • Intensive insulin therapy (among those aged >15) • Frequent blood glucose monitoring *Frequency of severe hypoglycemia (multivariate)* • Low HbA1c • Intensive insulin therapy (all ages)
Ter Braak et al.[101]	2000	195	Type 1	Retrospective clinical survey of consecutive patients using a questionnaire Primary outcome = severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	*Univariate factors* • Presence of neuropathy • Worry about hypoglycemia • Reduced hypoglycemic awareness *Multivariate factors* • Presence of nephropathy • Reduced hypoglycemic awareness • Insulin dose >0.1 U/kg higher
Muhlhauser et al.[102]	1998	684	Type 1	Prospective population-based survey Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = help required from others or hypoglycemic coma	*Multivariate factors* • Severe hypoglycemia in preceding year • Severe hypoglycemia anytime in the past • C-peptide negativity • Social status • Patient drive to attain normoglycemia
Bott et al.[103]	1997	636	Type 1	All patients were on intensive insulin therapy Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported)	Severe hypoglycemia = hypoglycemia requiring treatment with IV glucose or glucagon injection	*Multivariate factors* • Lower HbA1c during followup • Severe hypoglycemia in preceding year • C-peptide levels >0.1nmol/L • Younger age at onset of disease • Not carrying emergency glucose • Poorer scores on coping scale
Gold et al.[104]	1997	60	Type 1	Prospective Primary outcome = the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using structural equation modeling	Severe hypoglycemia = help required from others or hypoglycemic coma	*Multivariate factors* • Previous hypoglycemia • Age • Duration of disease • Reduced autonomic function • Reduced hypoglycemic awareness
Shorr et al.[105]	1997	19,932	Type 1 and type 2 On insulin or sulfonylureas (≥65 years old-Medicaid population)	Prospective Primary outcome = the number of serious hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Serious hypoglycemia = event that occurred outside of hospital that resulted in a visit to an emergency department, admission to hospital, or death	*Multivariate factors* • Age • Time since discharge from hospital • African-American race • Concomitant use of ≥5 medications • New hypoglycemic drug therapy

Reference	Year	N=	Diabetes Type	Study Details	Definitions Used	Risk Factors Identified
Pampanelli et al.[106]	1996	112	Type 1 (all IIT)	Prospective Primary outcome=the number of severe hypoglycemic episodes during a 13 year period Data analyzed using univariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Lower HbA1c • Reduced autonomic function • Reduced hypoglycemic awareness
Bell et al.[107]	1994	211	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Case-control design	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of disease • Number of insulin injections per day • Number of glucose tests per day • Presence of neuropathy and nephropathy • Use of animal insulin • Meal skipping;
EURODIAB[108]	1994	3,250	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of disease • Tight control
MacLeod et al.[16]	1993	600	Type 1 (n=544) Type 2[†] (n=54)	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Data analyzed using multivariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• History of hypoglycemia • History of hypoglycemia-related injury • Duration of insulin therapy • Frequency of outpatient reviews
Muhlauser et al.[109]	1991	90	All Type 1 Impaired kidney failure: (n=44)	Retrospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 year (self-reported) Case-control design	Severe hypoglycemia = hypoglycemia with loss of consciousness	• Impaired kidney function • Among patients with kidney impairment • Low BMI
Ward et al.[17]	1990	158	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 2 years (self-reported) Data analyzed using ANOVA	Severe hypoglycemia = help required from others or hypoglycemic coma	• None identified
Casparie & Elving[110]	1985	400	Type 1 (n=200) Type 2 (n=200) All treated with insulin	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1	Severe hypoglycemia = help required from others or hypoglycemic coma	• Type of diabetes (type 1 highest risk) • Low HbA1c • High dose of insulin

Reference	Year	N=	Diabetes Type	Study Details	Definitions Used	Risk Factors Identified
				year (self-reported)		
Goldgewicht et al.[111]	1983	172	Type 1	Prospective Primary outcome= the number of severe hypoglycemic episodes during the previous 1 to 5 years (self-reported) Data analyzed using univariate regression	Severe hypoglycemia = help required from others or hypoglycemic coma	• Duration of diabetes • Duration on insulin • Body mass index • Frequency of urine sample analysis • Frequency of blood sample analysis

Figure 12: Frequency Factor Identified as a Risk Factor for Hypoglycemia



4.3.2. Incidence of Severe Hypoglycemia with Treatment Associated Factors

Most available information on the frequency of the occurrence of hypoglycemia among patients who undergo treatment for diabetes comes from efficacy and safety studies (usually randomized controlled trials). Although randomized controlled trials (RCTs) are often considered, "the gold standard cohort study," when used to assess treatment efficacy and safety of a treatment, RCTs have a number of shortcomings, including the following:

1. Safety and effectiveness trials tend to enroll carefully screened and selected patients who are not representative of the broader population.
2. Safety and efficacy trials use protocols that are not reflective of disease management in the broader population.
3. Safety and effectiveness trials tend to be small and short-term, which precludes an accurate determination of the true incidence of hypoglycemia.

With the above limitations in mind, Table 31 identifies data obtained from systematic evidence reviews and/or meta-analyses regarding the impact of different treatments and treatment modalities on the incidence or occurrence of severe hypoglycemia. The key findings from the studies listed in the table are presented at the end of this subsection.

Table 31: Incidence or Occurrence of Severe Hypoglycemia Associated with Variable Treatments and Treatment Modalities

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
INSULIN-TREATED -- General						
Akram, K., U. Pedersen-Bjergaard, et al. (2006). "Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey." J Diabetes Complications 20(6): 402-408. [94]	Conduct a literature review to assess the rate of severe hypoglycemia and to evaluate the impact of potential risk factors	Type 2	Insulin (type varied)	464 papers retrieved/ 11 included	5 retrospective (n=1,122) 6 prospective (n=1,711) Inclusion Criteria: ≥6 month duration of study 50+ subjects Adults 19 years or older Insulin-treated	Incidence of SH in the retrospective studies: proportion of the patients having one or more episodes of SH per year was between 1.4 to 15%. Incidence of SH in the prospective studies: both incidence rate and proportion of the patients having one or more episodes of SH were lower than in the retrospective studies (0.0 to 2.3%). Identified Risk Factors for SH: • Impaired hypoglycemia awareness • High age • Longer duration of diabetes • Longer duration of insulin therapy
INSULIN-TREATED – Types of Insulin						
Short-Acting Analogues vs. Regular Human Insulin						
Mannucci, E., M. Monami, et al. (2009). "Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis." Diabetes Obes Metab 11(1): 53-59. [112]	To compare the impact of short-acting insulin analogues vs. regular human insulin on hemoglobin A1c (HbA1c)	Type 2	Short-acting insulin analogues (lispro, aspart or glulisine)	13 randomized controlled trials (RCTs); 7 with lispro, 4 Aspart, 2 glulisine	Mean age range 42-66; duration range of type 2 diabetes, 8-17 years; HbA1c % range, 7.4%-10.4%; BMI 25.4 - 34.5 kg/m²	In type 2 diabetic patients, short-acting insulin analogues provide a better control of HbA1c and postprandial glucose than regular human insulin, without any significant reduction of the risk of severe hypoglycemia. 13 patients receiving short-acting analogues and 21 with regular human insulin experienced severe hypoglycemia in 5 of the trials. Of these 5 trials, the Mantel–Haenszel odds ratio for severe hypoglycemia with short-acting analogues, in comparison with human insulin, was 0.61 (0.25-1.45). Short-acting analogues were not significantly different from regular human insulin with regard to severe hypoglycemia.
Siebenhofer A., J Plank et al (2009). "Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus" Cochrane Database Systematic Reviews 2006, Issue 2	To assess the effects of short-acting insulin analogues versus regular human insulin	Type 1 and type 2	Insulin analogues Regular human insulin	8,274 patients (49 studies)	People of any age or sex with type 1 or type 2 diabetes on insulin, and diabetic pregnant women (including gestational diabetes), mostly using the diagnostic criteria valid	Overall hypoglycemia: the results obtained with short-acting insulin analogues and regular insulin were comparable.

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
Art. No.:CD003287. DOI: 10.1002/14651858.CD003287.pub4. [113]					at the time of beginning the trial Breakdown N/A	
Long-Acting Analogues vs. Regular Human Insulin						
Monami, M., N. Marchionni, et al. (2009). "Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis." Diabetes Obes Metab 11(4): 372-378. [114]	Conduct a meta-analysis to assess the differences with respect to HbA1c (Glycated hemoglobin), incidence of hypoglycemia, and weight gain, between NPH human insulin and each long-acting analogue	Type 1	protamine Hagedorn (NPH) human insulin; glargine and detemir (long-acting insulin analogues)	285 studies retrieved/20 included	Mean age range, 11-42.9; duration range of type 2 diabetes, .3-18.5 years; HbA1c baseline range, 6.8-8.8%	The incidence of severe hypoglycemia was reported by 17 trials. 264 analogue and 225 NPH patients experienced at least 1 episode, respectively. Long-acting analogues were associated with a reduced risk for nocturnal and severe hypoglycemia.
Bazzano, L. A., L. J. Lee, et al. (2008). "Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials." Diabet Med 25(8): 924-932. [115]	Systematically analyze evidence from RCTs examining the safety and efficacy of neutral NPH insulin and glargine (long acting) in the management of adults with Type 2 diabetes. Secondary outcome of interest: hypoglycemic events	Type 2	Insulin (glargine vs. NPH)	12 RCTs/ 4,385 patients	54.1% male, mean age 58.3, mean BMI 28.4 kg/m², mean duration of diabetes 10.5 years The average length of studies was 27.8 weeks, with a range of 4 to 52 weeks, and average study size was 366 participants with a range of 24 to 756 participants	Mean percentages of participants reporting any (59.0 vs. 53.0%, P<0.001), symptomatic (51.4 vs. 42.9%, P<0.001) and nocturnal hypoglycemia (33.3 vs. 19.1%, P<0.001) were significantly greater among participants using NPH insulin than those taking glargine, respectively. The mean percentages of participants experiencing severe hypoglycemia (2.5 vs. 1.4%, P = 0.07) were not significantly different between glargine and NPH insulin.
Monami, M., N. Marchionni, et al. (2008). "Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis." Diabetes Res Clin Pract 81(2): 184-189. [116]	Meta-analysis to assess the differences with respect to HbA1c, incidence of hypoglycemia, and weight gain, between NPH human insulin and each long-acting analogue	Type 2	NPH insulin; detemir or glargine (long-acting insulin analogues)	151 studies retrieved/14 included	Mean age range, 56-61; duration range of type 2 diabetes, 7.1-13.7 years; HbA1c baseline range, 7.1-9.6%	The incidence of severe hypoglycemia was reported by all but five trials. 32 analogue and 36 NPH patients experienced at least 1 episode, respectively. Long-acting analogues are associated with a significant reduction in the rate of overall, nocturnal, and symptomatic hypoglycemia.

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
Horvath, K., K. Jeitler, et al. (2007). "Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus." Cochrane Database Syst Rev(2): CD005613. [117]	To assess the effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared with NPH insulin in patients with type 2 diabetes mellitus. Pooling of studies by means of random-effects meta-analyses was performed.	Type 2	Insulin glargine and insulin detemir compared with NPH	Within 8 studies, 1,715 insulin glargine patients and 578 insulin detemir patients were randomized	6 studies comparing insulin glargine with NPH insulin and 2 studies comparing insulin detemir with NPH insulin	No significant difference for severe hypoglycemia rates was shown in any of the trials. The rate of symptomatic, overall, and nocturnal hypoglycemia was significantly lower in patients treated with either insulin glargine or detemir.
Rosenstock, J., G. Dailey, et al. (2005). "Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes." Diabetes Care 28(4): 950-955. [118]	To compare insulin glargine (long-acting) with human NPH insulin in type 2 diabetes by meta-analysis	Type 2	Insulin glargine NPH insulin	4 studies 2,304 patients	Insulin glargine Men: 636 Women: 506 Age: 58.0±9.8 years BMI (kg/m²)=30.5±4.9 Age at onset of diabetes: 48.4±9.7 Diabetes duration: 10.2 ± 7 (years) NPH insulin Men: 652 Women: 510 Age: 58.4±9.3 years BMI (kg/m²)=30.5±6.4 Age at onset of diabetes: 48.4 ± 9.7 Diabetes duration: 10.6 ± 6.9 years	Insulin glargine given once daily reduces the risk of hypoglycemia compared with NPH insulin, which can facilitate more aggressive insulin treatment to a HbA1c target of ≤7.0% in patients with type 2 diabetes.
INSULIN-TREATED – Delivery Mechanism (Inhaled, Continuous Subcutaneous Infusion vs. Multiple Daily Injections)						
Misso, M. L., K. J. Egberts, et al. (2010). "Continuous subcutaneous insulin	To assess the effects of CSII compared with multiple insulin injections (MI) in people	Type 1 mellitus	Insulin	23RCTs	In the 23 studies, 976 participants with type 1 diabetes were randomized to	Severe hypoglycemia appeared to be reduced in those using CSII. Data indicate that CSII may be better than MI for reducing

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus." Cochrane Database Syst Rev(1): CD005103. [119]	with type 1 diabetes mellitus				continuous subcutaneous insulin infusion or multiple injections. 7 studies were performed in participants under 18 years of age; remainder were performed in adults. Study duration range - 6 days to 4 years	the incidence of severe hypoglycemic events.
Fatourechi, M. M., Y. C. Kudva, et al. (2009). "Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections." J Clin Endocrinol Metab 94(3): 729-740. [120]	To summarize evidence on the effect of CSII and MDIs on glycemic control and hypoglycemia	Type 1 and type 2	CSII compared with MDI	15 eligible randomized trials of moderate quality	13 studies examined type 1 diabetes; 2 studies examined type 2 diabetes	Severe hypoglycemia: Patients with type 1 diabetes using CSII had slightly lower HbA1c [random-effects weighted mean difference, -0.2%; 95% CI, -0.3, -0.1, compared with MDI], with no significant difference in severe (pooled odds ratio, 0.48; 95% CI, 0.23, 1.00), although the trend favored CSII. Outcomes were not different in patients with type 2 diabetes (OR=0.64; 95% CI, 0.12-3.28). Nocturnal hypoglycemia: There was no significant difference between study arms with the point estimate favoring CSII (OR= 0.82; 95% CI, 0.33-2.03) in trials of patients with type 1 diabetes (Fig. 4); the same was true in trials of patients with type 2 diabetes (OR=0.61; 95% CI, 0.26-1.47).
Jeitler, K., K. Horvath, et al. (2008). "Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis." Diabetologia 51(6): 941-951. [121]	To summarize evidence on the effect of CSII and MDIs on glycemic control and hypoglycemia	Type 1 and type 2	CSII compared MDI	22 publications	17 on type 1 diabetes mellitus, 2 on type 2 diabetes mellitus, 3 on children	No overall conclusions were possible for severe hypoglycemia and adverse events for any of the different patient groups due to rareness of such events, different definitions and insufficient reporting. 4 of 17 studies did not mention severe hypoglycemic episodes. 3 others reported that no severe hypoglycemia was observed. No information was provided on severe hypoglycemic episodes in 6 studies, and 4 reported on the rates/number of severe hypoglycemic events in treatment groups.
Pickup, J. C. and A. J. Sutton (2008). "Severe	To summarize evidence on the effect of CSII and	Type 1	CSII) compared with MDI	22 studies		Severe hypoglycemia was reduced during CSII compared with MDI, with a rate ratio of 2.89 (95% CI 1.45 to 5.76) for

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion." Diabet Med 25(7): 765-774. [122]	MDIs on glycemic control and hypoglycemia					RCTs and 4.34 (2.87 to 6.56) for before/after studies [rate ratio 4.19 (2.86 to 6.13) for all studies]. The reduction was greatest in those with the highest initial severe hypoglycemia rates on MDI (P < 0.001).
INTENSIVE VS. STANDARD GLYCEMIC CONTROL						
Zhang, C. Y., A. J. Sun, et al. (2010). "Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis." Ann Med 42(4): 305-315. [123]	To assess the effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes	Type 2	N/A	34,144 (7 trials)	Age: 59 years Duration: 6.47 years Mean HbA1c (%): 8.11	Intensive glucose control significantly reduced major cardiovascular events by 10% (relative risk (RR)=0.90, 95% CI 0.85 – 0.96; *P* = 0.0006), and non-fatal myocardial infarction by 16% (RR=0.84, 95% CI, 0.76 – 0.93; *P* = 0.0006) at the expense of increased incidence of severe hypoglycemia (RR=2.30, 95% CI, 1.74 – 3.03; *P* = 0.00001), while all-cause mortality, cardiovascular death, non-fatal stroke, and heart failure were similar between the two groups. A trend of greater decrease in the risk of major cardiovascular events was found in patients with shorter history of diabetes mellitus.
Ma, J., W. Yang, et al. (2009). "The association between intensive glycemic control and vascular complications in type 2 diabetes mellitus: a meta-analysis." Nutr Metab Cardiovasc Dis 19(9): 596-603. [124]	To perform a meta-analysis on the relationship between lowering HbA1c and vascular complications in patients with type 2 diabetes mellitus in order to better understand the relationship between major vascular events reduction and intensive glycemic control	Type 2	GLI; MET; TZD; SU; ROS; MIT; PIO	797 studies retrieved/ 8 included	RCTs comparing the effects of intensive and standard glycemic control on vascular events in patients with type 2 diabetes mellitus	Results showed a higher rate of severe hypoglycemia in the intensive control group when the target HbA1c level was <7.0%. When the target HbA1c level was lowered to 7.0-7.9%, intensive glycemic control showed benefits on the reduction of microvascular events without increasing the risk of severe hypoglycemia but no influence on macrovascular complications.
SELF-MONITORING OF BLOOD GLUCOSE						
Allemann, S., C. Houriet, et al. (2009). "Self-monitoring of blood glucose in non-insulin-	Assess the effect of Self-monitoring of blood glucose (SMBG) on glycemic control in non-	Type 2	SMBG in non-insulin-treated patients	7 of 15 included trials examined	Study duration varied from 3 months to 1 year	A total number of 268 hypoglycemic events were recorded -all graded as mild to moderate with the exception of one serious event.

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
treated patients with type 2 diabetes: a systematic review and meta-analysis." Curr Med Res Opin 25(12): 2903-2913. [125]	insulin- treated patients with type 2 diabetes by means of a systematic review and meta-analysis			rates of hypo-glycemia		SMBG significantly increased the probability to detect hypoglycemia.
Towfigh, A., M. Romanova, et al. (2008). "Self-monitoring of blood glucose levels in patients with type 2 diabetes mellitus not taking insulin: a meta-analysis." Am J Manag Care 14(7): 468-475. [74]	Assess the effect of SMBG on glycemic control in non-insulin-treated patients with type 2 diabetes	Type 2	SMBG in non-insulin-treated patients	9 RCTs (3 examined hypo-glycemic outcomes	All patients had type 2 diabetes with mean durations of 3 to 13 years.	Three trials reported hypoglycemic outcomes, which were increased in the patients using SMBG, although this mostly involved asymptomatic or mild episodes.

Some key findings emerge from the studies included in Table 31 above.

Types of Insulin

- *Short-acting insulin analogues*: In two meta-analyses (one of which was a Cochrane review) collectively looking at more than 50 RCTs, there was no difference in the occurrence of severe hypoglycemia in type 1 and type 2 patients taking short-acting insulin analogues compared with regular human insulin.
- *Long-acting insulin analogues*: In four of five systematic evidence reviews, summarizing comparisons of long-acting analogues (i.e., insulin glargine and/or detemir) with regular human insulin, significant reductions in the rate of severe hypoglycemia were observed. In all five studies, the incidence of nocturnal hypoglycemia was significantly reduced with long-acting analogues.

Delivery of Insulin

- *Continuous subcutaneous insulin infusion (CSII)*: There were mixed results with regard to CSII when compared with multiple daily injections in reducing the incidence of severe hypoglycemia. Two studies, including a 2010 Cochrane review, found that CSII does significantly reduce the incidence of severe hypoglycemia. In other reviews, where the results were not significant, there was a trend toward a reduction in severe hypoglycemia in type 1 patients using CSII compared with multiple daily injections.

Intensive vs. Standard Glycemic Control

- *Intensive Glycemic Control*: In a 2010 meta-analysis of seven trials consisting of more than 34,000 patients, intensive glucose control was found to significantly reduce cardiovascular events in patients with type 2 diabetes. Similarly, in another 2009 meta-analysis, intensive glycemic therapy significantly reduced microvascular complications. In both of these meta-analyses, the incidence of severe hypoglycemic events was significantly increased. However, it was also demonstrated that intensive glycemic therapy that aimed to keep HbA1c levels between 7.0 and 7.9 percent did not increase the risk for severe hypoglycemia in patients with type 2 diabetes, and was still associated with reduced microvascular complications.

Monitoring Glucose Levels

- *Self-Monitoring of Blood Glucose (SMBG)*: In two recent meta-analyses of the effect of SMBG in non-insulin treated patients with type 2 diabetes, SMBG was found to be associated with significant increases in the rate of hypoglycemia.

4.3.3. Injectable, Non-Insulin Drugs for Type 2 Diabetes

In this subsection, we summarize evidence obtained from recent reviews regarding the safety and effectiveness of newer non-insulin-based injectable drugs for diabetes. There are currently three non-insulin injectable drugs used to treat type 2 diabetes.

- Pramlintide
- Exenatide

- Liraglutide

Pramlintide (Symlin®) is a synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. Amylin, insulin, and another hormone, glucagon, work in an interrelated fashion to maintain normal blood glucose levels.

Pramlintide injections are taken with meals along with insulin, and have been shown to modestly improve HbA1c levels and promote modest weight loss. The primary side effect is nausea, which tends to improve over time and as an individual patient determines his or her optimal dose.

Pramlintide has been approved for people with type 1 diabetes who are not achieving their goal HbA1c levels and for people with type 2 diabetes who are using insulin and are not achieving their HbA1c goals.

Exenatide (Byetta®) is the first in a new class of drugs for the treatment of type 2 diabetes called incretin mimetics. Exenatide is a synthetic version of exendin-4, a naturally occurring hormone that was first isolated from the saliva of the lizard known as a Gila monster. Exenatide works to lower blood glucose levels primarily by increasing insulin secretion. Because it only has this effect in the presence of elevated blood glucose levels, it does not tend to increase the risk of hypoglycemia on its own, although reports show that hypoglycemia can occur if taken in conjunction with a sulfonylurea. The primary side effect is nausea, which tends to improve over time.

Like pramlintide, exenatide is injected with meals and, as with pramlintide, patients using exenatide have generally experienced modest weight loss as well as improved glycemic control. Exenatide has been approved for use by people with type 2 diabetes who have not achieved their target HbA1c levels using metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

Liraglutide (Victoza®) is a long-acting glucagon-like peptide-1 (GLP-1) analog that has been developed by Novo Nordisk for the treatment of type 2 diabetes. The product was approved by the European Medicines Agency (EMEA) on July 3, 2009, and by the FDA on January 25, 2010.

Like exenatide, liraglutide is a non-insulin-based injectable drug used to treat individuals with type 2 diabetes. Preliminary review of studies suggests that liraglutide is useful in improving glycemic control and reducing weight in people with type 2 diabetes. It also appears to be associated with fewer hypoglycemic events.

The primary concern with both liraglutide and exenatide is the occurrence of severe hypoglycemia with their use. There are a number of systematic reviews available to address exenatide and one or more that deal with the use of liraglutide. A summary of these reviews is provided in Table 32.

Table 32: Incidence or Occurrence of Severe Hypoglycemia Associated with Variable Treatments and Treatment Modalities

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
OTHER, NON-INSULIN INJECTABLE						
Hansen, K. B., F. K. Knop, et al. (2009). "Treatment of type 2 diabetes with glucagon-like peptide-1 receptor agonists." Int J Clin Pract 63(8): 1154-1160. [126]	To review the new glucose homeostasis treatment modality: Glucagon-like peptide-1 (GLP-1)	Type 2	Exenatide and liraglutide	NA; qualitative review	6 exenatide clinical trials; 6 Liraglutide Effect and Action in Diabetes (LEAD) clinical trials	The incidence of hypoglycemia with GLP-1 receptor agonists is low.
Norris, S. L., N. Lee, et al. (2009). "Exenatide efficacy and safety: a systematic review." Diabet Med 26(9): 837-846. [127]	To examine the efficacy, effectiveness and side effects of exenatide when compared with oral glucose-lowering agents or insulin therapy	Type 2	Exenetide insulin glargine	4, active controlled trials 4, placebo controlled trials	17 studies were indentified	Rates of hypoglycemia were similar in exenatide and insulin groups, but were higher with exenatide 10 micrograms twice daily compared with placebo, and hypoglycemia was most frequent when a sulphonylurea was administered.
Aggressive Research Intelligence Facility (ARIF) (2008) Literature search on the risk of hypoglycemia in patients with type 2 diabetes treated with sulphonylureas with or without exenatide. [76]	To determine: 1) The risk of hypoglycemic events in diabetic patients being treated with sulphonylureas (SFU)+ exenatide + any other treatment (including no treatment) except insulin 2) The risk of hypoglycemic events in diabetic patients being treated with SFUs + any other treatment (including no treatment) except exenatide or insulin	Type 2	Exenatide and liraglutide	7 relevant reviews were summarized. 5 RCTs were included in the reviews and summarized in this report	Reviews were of low to moderate quality (1 was a high-quality review)	Primary findings for sulphonylurea with exenatide • Hypoglycemic episodes per patient-year ranged from 4.1 to 7.3. • Incidence of hypoglycemia ranged from between 14% and 30% (the 30% finding was based on a relatively small subgroup of patients [n=62] only). • Severe hypoglycemic episodes were observed in 1 and 4 patients (2 trials respectively) or not at all (3 trials). • Where reported (2 trials) incidence of hypoglycemia was higher in those patients taking a higher dose of exenatide; comparisons within an RCT are likely to provide the best evidence on differences between doses. It should be noted, however, that confidence intervals are not reported and the studies were not specifically powered to detect a difference between hypoglycemia rates with different dosages. • Pooled data from open-label extensions (up to 82 weeks) of 2 trials found incidences of between 8% and 15% (exenatide arm only).

Reference	Objective	Type	Treatment Factors	Number of Included Studies	Description of Included Studies	Results Regarding the Incidence of Severe Hypoglycemia (SH)
						• Where there was a comparison arm consisting of patients taking an SFU (two trials), incidences (3% and 12.6%) were lower than in those patients taking an SFU with exenatide. • In 2 trials, patients were not eligible if they had experienced more than 3 episodes of severe hypoglycemia within 6 months before screening; it is unclear whether trial populations are representative of all patients who could be eligible for this type of treatment.

4.3.4. Findings

4.3.4.1. Summary of Findings Regarding Risk Factors Associated with Incidence of Severe Hypoglycemia

As demonstrated in Figure 12: Frequency Factor Identified as a Risk Factor for Hypoglycemia, presented at the beginning of this section, a number of risk factors have been repeatedly shown to be associated with an increased incidence of severe hypoglycemia (summarized in Table 33, below). These include the following behavioral, demographic, and treatment-related risk factors:

Table 33: Risk Factors for Severe Hypoglycemia

Behavioral	Demographic	Treatment
• Meal skipping/dieting • Exercise • Alcohol use	• Impaired hypoglycemia awareness • Long duration of disease • Advancing age • Previous hypoglycemia • Neuropathy • Gender	• Long duration of insulin therapy • Lower HbA1c levels • Intensive insulin therapy • Higher insulin dose • Higher number of daily injections

4.3.4.2. Summary of Findings Regarding Treatment Factors Associated with Severe Hypoglycemia

A high-level overview of systematic evidence reviews regarding various treatment-related factors that have been shown to be associated with either increased are decreased incidence of severe hypoglycemia was provided. As noted in this section, some key findings emerge from the studies included in Table 31 above:

- There is little difference in the occurrence of severe hypoglycemia in type 1 and type 2 patients taking short-acting insulin analogues compared with regular human insulin. Contrary to this, the use of long-acting analogues (i.e., insulin glargine and/or detemir) compared with regular human insulin has been shown to result in significant reductions in the rate of severe hypoglycemia.
- A review of published meta-analyses revealed mixed results with regard to CSII when compared with multiple daily injections in reducing the incidence of severe hypoglycemia. However, the results of these studies suggest a trend toward a reduction in severe hypoglycemia in type 1 patients using CSII compared with multiple daily injections.
- Two recent meta-analyses clearly show the benefit of tight or intensive glycemic control in reducing long-term complications in patients with type 2 diabetes. However, the incidence of severe hypoglycemic events is also significantly increased.
- SMBG in non-insulin treated patients with type 2 diabetes was found to be associated with significant increases in the rate of hypoglycemia.

4.3.4.3. Summary of Findings Regarding Injectable, Non-Insulin Drugs & UK Driving Requirements

Trials published to date show a small but significant risk of hypoglycemia when exenatide is used in conjunction with a sulphonylurea. It would also appear that when the gliptins (DPP4 inhibitors) or liraglutide are used with sulphonylureas, the hypoglycemia risk is similarly raised.

According to the DVLA in the United Kingdom, the increased risk of hypoglycemia from exenatide, liraglutide, or gliptins when used in combination with sulphonylureas is such that these are felt to be a potentially high-risk treatment for drivers holding Group 2 (large goods vehicle or passenger carrying vehicle) licenses and that individual assessment will of these drivers is required.

Group 2 drivers are required to notify the DVLA if they have diabetes treated with tablets. If they are then started on exenatide, liraglutide, or a gliptin, they are only required to notify DVLA if this is in combination with a sulphonylurea because of the increased risk that has been found to be associated with this combination.

The use of exenatide, liraglutide, or gliptins currently carries no specific driving restrictions for Group 1 (car or motorcycle) licenses in the UK.

4.4. Key Question 4: How Effective is Hypoglycemia Awareness Training in Preventing the Consequences of Hypoglycemia?

In the 2006 version of this report, Key Question 4 evaluated the evidence pertaining to the effectiveness of hypoglycemia awareness training. In particular, our review focused on training protocol developed by Cox and his colleagues at the University of Virginia, called Blood Glucose Awareness Training (BGAT). BGAT is a psychoeducational intervention program designed to assist individuals with type 1 diabetes in managing and maintaining tight diabetic control.[128] According to the program's developers, individuals need accurate information about how their insulin, dietary choices, and physical activity levels affect their blood glucose in order to effectively manage their diabetes.[128] In addition, it is argued that for individuals with diabetes to manipulate these factors to achieve euglycemic balance, they must know where their blood glucose level is and be able to determine which direction it is going. For example, a blood glucose level of 3.3 mmol/L (60 mg/dl) that is rising may need no intervention, but a blood glucose level of 3.5 mmol/L (65 mg/dl) that is rapidly falling may require immediate intervention in order to avoid hypoglycemia.

BGAT is an eight-week program centered on a manual[4] that consists of eight distinct units. Unit 1 focuses on how to apply BGAT to daily life through homework, including making use of a blood glucose awareness diary. Patients observe and record any blood glucose-relevant cues in the diary, estimate their perceived blood glucose level based on these cues, compare these estimates to an actual measured blood glucose level, and then calculate the accuracy of their estimated blood glucose level using an error grid. This process is repeated throughout BGAT with the aim of refining the accuracy of the patient's perceived blood glucose level. Units 2 through 4 of the BGAT program focus on the recognition and interpretation of three critical aspects of blood glucose self-management — carbohydrate counting, insulin kinetics, and metabolic equivalents of physical activity — thereby providing the patient with a better understanding of why their blood glucose level is where it is and what changes in this level are likely to occur in the near future. Units 5 through 7 aim to teach users to recognize and interpret internal indicators of blood glucose extremes (autonomic symptoms, glycopenic symptoms, mood changes, etc.). Unit 8 summarizes what has been learned during the previous seven weeks of the program and promotes relapse prevention.

Based on additional research, Cox and his colleagues adapted BGAT[129-131] into the "Hypoglycemia Anticipation, Awareness and Treatment Training (HAATT)" program.[128, 132] Like its predecessors, HAATT is an eight-unit program; however, HAAT differs from BGAT-1 and BGAT-2 in that it is focused specifically on treating individuals suffering from recurrent severe hypoglycemia. HAATT and BGAT were later consolidated into a single program, BGAT-3.

According to Cox,[128] a major barrier to the dissemination of BGAT and HAATT is the availability of training and materials. Consequently, Cox and his colleagues transformed the

[4] Five different versions of the BGAT manual have been published (BGAT-1, BGAT-2, HAATT, BGAT-3, and BGATHome.com). Despite differences between the manuals, the basic structure of the program remains the same. The most obvious differences in the programs result from a progressive inclusion of items such as observation of external cues, implementation of newer insulin therapies as they became available, and an emphasis on long-term BG maintenance.

program so that it could be delivered on the internet (www.BGATHome.com). Unlike previous iterations of BGAT, BGATHome.com is a seven- (not eight-) unit program. Each unit of this interactive program takes between 15 and 60 minutes to complete.

In the 2010 update for this key question, a 2008 study by Cox and colleagues was identified pertaining to the BGATHome program in which BGATHome was evaluated by 40 type 1 diabetic participants over the course of 12 weeks.[133] It was the first time BGAT was made available to individuals with various goals, needs, diabetes regimens, and resources and despite the diversity, BGATHome resulted in significant clinical improvements ($P< 0.05$). It was judged as useful and easy to use, having been completed by 94 percent of the participants. Overall, it was found that the benefits of disseminating BGATHome over the internet, in a personalized and self-directed format, served a large number of individuals in a cost-effective manner.

In addition to the recent Cox study, another article relevant to this section was found in the present search. The article, "The decision not to drive during hypoglycemia in patients with type 1 and type 2 diabetes according to hypoglycemia awareness," examined the relationship between diabetes and driving. Researchers surveyed 24 type 1 diabetic patients with normal awareness of hypoglycemia (T1Norm group), 21 type 1 diabetic patients with impaired awareness of hypoglycemia (T1Imp group), and 20 type 2 diabetic patients with normal awareness of hypoglycemia (T2 group) to determine if the individuals would drive while feeling hypoglycemic and whether they would drive during experimental euglycemia/hypoglycemia. It was found that both the T1Imp and T2 groups frequently decided to drive while hypoglycemic, whereas the T1Norm group appeared to make safer decisions concerning hypoglycemia and driving. This is the first study to examine the decision to drive in diabetic patients according to objectively assessed hypoglycemia awareness and the first experimental study with type 2 diabetic patients.

Our updated search of the literature regarding hypoglycemic awareness training did not identify any new studies that met inclusion criteria that addressed BGAT. However, one comparable study was identified that examined the effectiveness of an alternative hypoglycemia awareness training program call HyPOS. HyPOS is a specific education training program designed for type 1 diabetic patients with impaired hypoglycemia awareness. Developed by researchers at Germany's Research Institute of the Diabetes Academy Mergentheim and the University of Greifswald's Institute of Psychology, HyPOS focuses on "avoiding low blood glucose values, informing patients about the causes of hypoglycemia unawareness, modifying health beliefs that contribute to frequent low blood glucose readings, improving the detection and recognition of hypoglycemic warning symptoms, and emphasizing the need for immediate and sufficient treatment of low blood glucose values" (Hermanns 2007). It consists of five lessons, once a week, with each lesson lasting approximately 90 minutes. Lessons 1 and 2 focus on providing a better understanding of hypoglycemia problems and increasing hypoglycemia awareness through the use of patient diaries, hypoglycemia checks and target control. Lesson 3 stresses the importance of immediate treatment of low blood glucose, while lesson 4 focuses on individual insulin therapy and coping with activities that may pose a risk of hypoglycemia. In the final lesson, participants are allowed to invite a family member or friend to further discuss coping with hypoglycemia-related issues, and the previous weeks' lessons are evaluated. Overall, the HyPOS program was found to provide

additional benefits to hypoglycemia education programs, specifically in regards to increasing participants' hypoglycemia awareness.

According to Hermanns et al.[134] HyPOS differs in several respects from BGAT. HyPOS contains less general diabetes education material (which is already contained in information that patients receive elsewhere), resulting in a shorter duration for training with HyPOS. In addition, the authors note that the German version of BGAT focuses on detection of both low and high blood glucose values; HyPOS focuses exclusively on low blood glucose values.

4.4.1. Identification Evidence Base

The development path of the evidence base for Key Question 4 is summarized in Figure 13: Development of Evidence Base Update for Key Question 4. For the 2006 report, our searches (Appendix A) identified a total of 82 articles that appeared to be relevant to this key question. Following application of the *a priori* retrieval criteria for this question (Appendix B), 26 full-length articles were retrieved and read in full. Of these 26 retrieved articles, seven articles were found to meet the inclusion criteria for Key Question 4 (Appendix B). Table B-3 of Appendix B lists the articles that met the *a priori* retrieval criteria for this question but that were found, on reading the full-length article, not to meet the inclusion criteria for this key question.

In the updated search, 16 articles were identified that pertained to Key Question 4. As previously done in 2006, we used the application of the *a priori* retrieval criteria to retrieve and thoroughly review all 16 full-length articles. Of these 16 retrieved articles, only one article was found to meet the inclusion criteria for Key Question 4.

Figure 13: Development of Evidence Base Update for Key Question 4

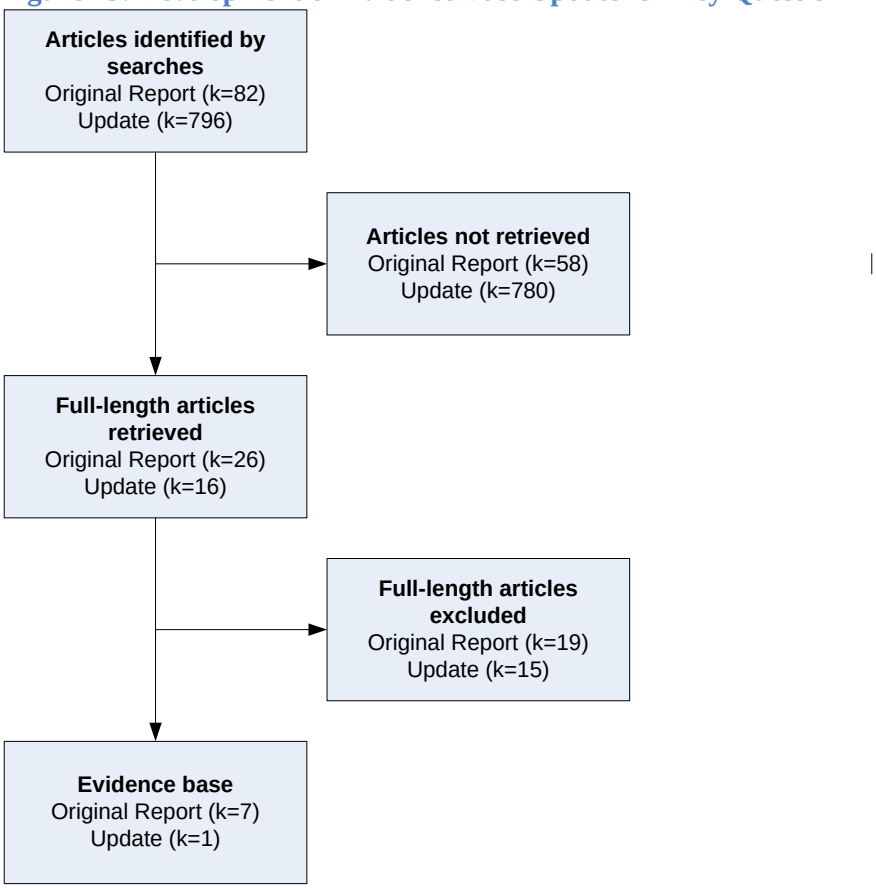


Table 34 lists the seven previous and one new study that met the inclusion criteria for Key Question 4.

Table 34: Evidence Base for Key Question 4

Reference	Year	Form of BGAT studied	Study Site(s)	Country
2010 Update				
Hermanns et al. [134, 135]	2007	HyPOS	23 Outpatient Study Centers: Dr. R.Betzholz, Neuss; Dr. R. Bickel, Pforzheim; Dr. B. Donaubauer, Oschatz; Dr. K. Drynda, Leipzig; Dr. G. Eberlein, Bayreuth; Dr. F. Ferara, Ludwigshafen; Dr. G. Hess, Worms; Dr. B. Kalvelage, Hamburg; Dipl-Med C. Kosch Parana; Dr. J. Kröger, Hamburg; Dr. M. Lederle, Stadtlohn; Dr. B. Lippmann-Grob, Offenburg; Dr. B. Oser, Bernkastel-Kues; Dr. D. Reichert, Landau; Dr. L. Rose, Münster; Dr. K. Rudolph, Langen; Dr. M. Schlotmann, Köln; Dr. B. Schulze-Schleppinghoff, Essen; Dr. T. Segiet, Speyer; Dr. M. Simonsohn, Frankfurt/Main; Dr. S. Vidal, Bad Mergentheim; Dr. G. von Bergmann, Lampertheim; Dr. J. Zimmermann, Würzburg	Germany
2006 Report				
Schachinger et al.[136]	2005	BGAT-2	Basal University Hospital; Olten Diabetes Clinic; Bad Mergentheim; Diabetes Outpatient Center Practice; Solurthurn Diabetes Outpatient Clinic; Aarau Diabetes Outpatient Clinic; Kanton Hospital Lozern	Switzerland and Germany
Cox et al.[132]	2004	HAATT	Medical University of Sofia, Sofia; Medical University of Varna, Varna; District Hospital, Russe	Bulgaria

Broers et al.[137, 138]	2002	BGAT-1	Leiden University Medical Center, Leiden	Netherlands
Kinsley et al.[139]	1999	BGAT-1	The Joslin Diabetes Center, Boston, Massachusetts	U.S.
Cox et al.[140]	1991	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	U.S.
Cox et al.[141]	1989	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	U.S.
Cox et al.[142]	1988	BGAT-1	University of Virginia Health Sciences Center, Charlottesville, Virginia	U.S.

4.4.2. Study Design Details

The design details of interest of the seven included studies from 2006 and the one included study from the present can be found in Table 35. All eight included studies that addressed Key Question 4 were prospective. Included studies used one of two general designs; randomized controlled trials (*k*=6) and non-randomized controlled trials (*k*=2). Three of the included studies were multicenter studies.

Table 35: Design of Included Studies (Key Question 4)

Reference	Year	Form of BGAT Studied	Size (N=)	Prospective?	Randomized?	Multicenter? (If yes, number centers)	Blinding Status	BGAT Attrition Rate (%)	Control Attrition Rate (%)	Follow-up Time (months)
Hermanns et al. [134, 135]	2007	HyPOS	164	Y	Y	Yes – 23	N	8.75 %	13.1%	6
Schachinger et al.[136]	2005	BGAT-2	138	Y	Y	Yes – 6	NR	23%	23%	12
Cox et al.[132]	2004	HAATT	60	Y	Y	Yes – 3	NR	NR	NR	12
Broers et al.[137, 138]	2002	BGAT-1	59	Y	N	N	N	28%	22%	12
Kinsley et al.[139]	1999	BGAT-1	47	Y	Y	N	NR	NR	NR	1
Cox et al.[140]	1991	BGAT-1	39	Y	Y	N	NR	NR	NR	2
Cox et al.[141]	1989	BGAT-1	22	Y	Y	N	NR	NR	NR	>1
Cox et al.[142]	1988	BGAT-1	16	Y	N	N	NR	NR	NR	>1

4.4.3. Quality of Evidence Base

The findings of our assessment of the quality of each of the seven included studies are presented in Table 36. Two included studies, the studies of Broers et al. and Schachinger et al., were found to be particularly susceptible to bias. Neither study demonstrated that it was protected against selection bias (a lack of comparability of individuals allocated to different arms of a study). Despite the fact that the study of Schachinger et al. was randomized, the comparability of treatment groups was compromised by a number of factors (high attrition rates, differential attrition, and evidence of possible randomization failure [non-comparability at baseline despite randomization]). As a consequence of the high potential for selection bias, one cannot have confidence that any between-group difference in outcome observed by either study was the result of BGAT. Such differences could simply be the result of systematic differences in the characteristics of the individuals enrolled in the two groups. As a result, we do not consider these two studies any further in this evidence report.

Table 36: Quality of Included Studies (Key Question 4)

Reference	Year	Form of Training Studied	Quality Scale Used	Acceptable Group Comparability?	Quality
Hermanns et al. [134, 135]	2007	HyPOS	EQS-I	Yes	Moderate
Schachinger et al.[136]	2005	BGAT-2	EQS-I	No	Not assessed
Cox et al.[132]	2004	HAATT	EQS-I	Yes	Moderate
Broers et al.[137, 138]	2002	BGAT-1	EQS-I	No	Not assessed
Kinsley et al.[139]	1999	BGAT-1	EQS-I	Yes	Moderate
Cox et al.[140]	1991	BGAT-1	EQS-I	Yes	Moderate
Cox et al.[141]	1989	BGAT-1	EQS-I	Yes	Moderate
Cox et al.[142]	1988	BGAT-1	EQS-I	Yes	Low
Overall quality					Moderate

4.4.4. Generalizability of Evidence to Target Population

The degree to which the findings of the studies that make up the evidence base for Key Question 4 may be generalized to individuals with diabetes who might consider a career as an interstate CMV operator is unclear.

Enrollment in all five of the 2006 studies addressing Key Question 4, as well as the one new study identified for the present update, was restricted to individuals with type 1 diabetes. Since hypoglycemic unawareness affects individuals with type 1 diabetes almost exclusively, the fact that BGAT has not been studied in populations of individuals with type 2 diabetes is to be expected.

Other important aspects of the patients enrolled in the included studies are presented in Table 37. As evidenced by the incompleteness of the table, the reporting of the characteristics of the enrollees in these five studies was poor, especially in the older studies. Basic patient demographic information such as age and sex were not consistently reported. Characteristics of particular interest to diabetes research such as mean HbA1c, body mass index, mean duration of disease, and mean daily insulin intake were also inconsistently reported. From the information that was reported, it appears that the majority of the patients enrolled in the included studies were between 23 and 49 years old, with males making up 33 percent to 54 percent of trial participants. No information on the employment status of study enrollees was presented.

Table 37: Characteristics of Enrollees (Key Question 4)

Reference	Year	Treatment Group	Sample Size: n=	Mean Age (SD): Years	Mean Duration of Disease (SD): Years	Percent Male	Mean HbA1c (SD)	Mean Daily Insulin Intake (SD): U/kg	BMI	Generaliz-ability
Hermanns et al. [134, 135]	2007	Overall	146	46.0 (12.5)	21.2 (10.08)	50.0	7.3 (1.0)	4.9 (1.1)	25.4 (3.7)	Unclear
		HyPOS	74	46.0 (11.7)	20.2 (10.8)	50.0	7.2 (0.9)	4.7 (0.9)	25.0 (3.0)	
		Control	72	45.9 (13.3)	22.1 (10.9)	50.0	7.4 (1.1)	5.0 (1.3)	25.8 (4.2)	

Cox et al.[132]	2004	Overall	60	38.06 (9.27)	13.96 (8.93)	53.0	8.04 (0.74)	44.75 (14.13)	23.17 (3.26)	Unclear
		BGAT	30	37.60 (9.00)	13.93 (9.33)	53.0	8.08 (0.74)	46.63 (14.91)	23.61 (3.44)	
		Control	30	38.62 (9.76)	14.00 (7.64)	54.0	7.98 (0.70)	42.30 (12.96)	22.63 (2.99)	
Kinsley et al.[139]	1999	Overall	47	34.0 (8.0)	9.0 (3.0)	48.9	9.0 (1.2)	NR (NR)	25 (3.0)	Unclear
		BGAT	25	NR (NR)	NR (NR)	NR	9.1 (1.4)	NR (NR)	NR (NR)	
		Control	22	NR (NR)	NR (NR)	NR	9.0 (1.1)	NR (NR)	NR (NR)	
Cox et al.[140]	1991	Overall	39	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT (Standard)	13	33.7 (NR)	13.0 (NR)	38.5	10.4 (NR)	0.65 (NR)	NR (NR)	
		BGAT (Intensive)	12	31.1 (NR)	12.7 (NR)	33.3	12.8 (NR)	0.67 (NR	NR (NR)	
		Control	14	33.8 (NR)	11.2 (NR)	35.7	11.4 (NR)	0.62 (NR)	NR (NR)	
Cox et al.[141]	1989	Overall	22	32.4 (8.5)	10.6 (7.7)	36.4	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT	15	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
		Control	7	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
Cox et al.[142]	1988	Overall	20	43.7 (NR)	10.3 (NR)	40.0	NR (NR)	NR (NR)	NR (NR)	Unclear
		BGAT	10	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	
		Control	10	NR (NR)	NR (NR)	NR	NR (NR)	NR (NR)	NR (NR)	

4.4.5. Findings for Key Question 4

The six included studies and the outcomes they reported on are listed in Table 38. Outcome data were available for only two of the outcomes of interest to us. Data on sensibility to driving capability while impaired, and the incidence of motor vehicle crash, were not presented by any of the included studies. Of the two remaining outcomes of interest, three studies (including the one new study identified in the current update) provided data on the incidence of severe hypoglycemia following BGAT, and all six studies reported on the accuracy with which individuals with type 1 diabetes could estimate their blood glucose levels based on internal cues.

Table 38: Outcomes Assessed (Key Question 4)

Reference	Year	Outcomes of Interest			
		Crash	Sensibility to Driving Capability while Impaired	Incidence of Severe Hypoglycemic Episodes	Blood Glucose Level Accuracy Index
Hermanns et al. [134, 135]	2007			✓	✓
Cox et al.[132]	2004			✓	✓
Kinsley et al.[139]	1999			✓	✓
Cox et al.[140]	1991				✓
Cox et al.[141]	1989				✓
Cox et al.[142]	1988				✓
Total # Studies		0	0	3	6

4.4.5.1. Blood Glucose Level Accuracy Index

All six included studies reported on the effect of BGAT on the ability of an individual with type 1 diabetes to accurately estimate blood glucose levels. Relevant results from these studies are presented in Table 39. Because the outcome data from three of the five studies were poorly presented, we have not attempted to calculate a precise estimate of the effectiveness of hypoglycemia awareness training in improving the accuracy of blood glucose level estimation. Accordingly, our analysis of the available evidence pertaining to this outcome is purely qualitative.

Four of the six included studies, all authored by Cox, found that BGAT was effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood sugar levels based on internal cues alone. In addition, the newly identified study found that another intervention, referred to as HyPOS, improves the ability of individuals with type 1 diabetes to accurately estimate their blood sugar levels The sixth study (Cox was listed as a co-author for this study) found no difference in the ability of individuals who had undergone BGAT to accurately estimate their blood glucose levels when compared with controls. However, the authors of the study reported that individuals who underwent BGAT demonstrated significantly greater improvements in their ability to detect low blood glucose levels. Consequently, the available evidence, though not strong, does consistently suggest that hypoglycemia awareness training is effective in improving the ability of individuals with type 1 diabetes to accurately estimate their blood glucose levels. Whether this improvement in the ability to estimate blood glucose levels has the net effect of reducing the incidence of severe hypoglycemia is addressed below.

Table 39: Effect of BGAT on Ability to Accurately Estimate Blood Glucose Levels

Reference	Year	Cohort	Blood Glucose (BG) Estimation Accuracy		Comments and Conclusions
			Mean (SD or SEM)	P(between groups)=	
Hermanns et al. [134, 135]	2007	HyPOS	Baseline: 2.5±0.7 Follow-up: 3.0±0.5	0.01	Evidence supports contention that HyPOS awareness training may improve BG estimation accuracy.
		Control	Baseline: 2.5±0.7 Follow-up: 2.8±0.6		
Cox et al.[132]	2004	HAATT	*Reduction in extreme BG fluctuations* Mean BG Risk Index: 12.8 (SD: 4.05) Percent accuracy of BG evaluation: 82%	<0.01 <0.001	Evidence supports contention that HAATT awareness training may improve BG estimation accuracy.
		SMBG	*Reduction in extreme BG fluctuations* Mean BG Risk Index: 17.9 (SD: 4.74) Percent accuracy of BG evaluation: 73%		

Kinsley et al.[139]	1999	BGAT	At 3.3 mmol/L: error=−3.7 (SEM: 1.2) At 2.8 mmol/L: error=−2.4 (SEM: 0.9) At 2.2 mmol/L: error=−1.1 (SEM: 0.5)	NS for any comparison BGAT had fewer undetected low BG readings compared with controls (P <0.05)	No evidence to support contention that BGAT improves overall blood glucose level awareness any more than a non-specific control. However, those subjects who underwent BGAT had fewer undetected low BG readings compared with controls.
		Cholesterol Ed.	At 3.3 mmol/L: error=−3.7 (SEM: 1.1) At 2.8 mmol/L: error=−2.1 (SEM: 0.9) At 2.2 mmol/L: error=−1.0 (SEM: 0.4)		
Cox et al.[140]	1991	Standard BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: P <0.0001 Group * Time interaction: P <0.001 S-BGAT vs I-BGAT: P=0.17	Evidence that BGAT awareness training may improve BG estimation accuracy when compared with non-specific control group. There was no significant difference between standard BGAT and intensive BGAT in improving BG estimation accuracy.
		Intensive BGAT	Mean Accuracy Index=NR (SEM: NR)		
		Control	Mean Accuracy Index=NR (SEM: NR)		
Cox et al.[141]	1989	BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: P=NS Group effect: P=NS Group * Time interaction: P=0.001	Evidence that BGAT awareness training may improve BG estimation accuracy.
		Control	Mean Accuracy Index=NR (SEM: NR)		
Cox et al.[142]	1988	BGAT	Mean Accuracy Index=NR (SEM: NR)	Time effect: P=0.037 Group * Time interaction: P=0.019	Evidence that BGAT awareness training may improve BG estimation accuracy when compared with a non-specific control group.
		Control	Mean Accuracy Index=NR (SEM: NR)		

4.4.5.2. Severe Hypoglycemic Event Rate

As discussed in the previous section, currently available evidence on the effectiveness of hypoglycemia awareness training (in all its forms) suggests that it may be effective in improving the ability of some individuals with type 1 diabetes to estimate their blood glucose levels. Limited data suggest that hypoglycemia awareness training may also improve blood glucose awareness in some individuals with hypoglycemic unawareness. If these findings are valid and hypoglycemia awareness training can achieve clinically significant effects, then one would expect that such training would reduce the incidence of severe hypoglycemic events among individuals with type 1 diabetes, because such individuals will be more aware of their glycemic status and, when necessary, better able to take corrective action to prevent the occurrence of severe hypoglycemia. The purpose of this subsection is to determine whether there is evidence to support this contention.

Three of the five included studies (that enrolled a total of 253 individuals) reported on the incidence of severe hypoglycemic episodes experienced by individuals with type 1 diabetes following exposure to hypoglycemia awareness training when compared with a control. Relevant outcome data from these studies are presented in Table 40. The findings of the two studies are inconsistent. One study observed a significant reduction in the incidence of severe hypoglycemic episodes while the other two studies did not. Other than noting that the three studies used slightly

different training programs, HyPOS and BGAT (HAATT and GBAT-1), and pointing out the slight differences in the enrollees in these studies, the inconsistencies in the findings of the three studies could not be satisfactorily explained. Given this, we conclude that, at this time, it remains unclear whether the apparent benefits of an improved ability to estimate blood glucose levels are expressed as measurable reductions in the incidence of severe hypoglycemia in individuals with type 1 diabetes.

Table 40: Effect of BGAT on Incidence of Severe Hypoglycemic Episodes

Reference	Year	Cohort	Severe Hypoglycemic Episodes		Conclusion
			Mean (SD or SEM)	P=	
Hermanns et al. [134, 135]	2007	HyPOS	0.3 episodes/person/month	NS	No evidence to support contention that HyPOS reduces the incidence of severe hypoglycemia in more effectively than does a non-specific control. However, the trend is toward improvement following HyPOS.
		Control	0.6 episodes/person/month		
Cox et al.(116)	2004	HAATT	0.4 episodes/person/month	P=0.03	Study provides evidence in support of the contention that HAATT reduces the incidence of severe hypoglycemia.
		SMBG	1.7 episodes/person/month		
Kinsley et al.(120)	1999	BGAT	0.69 (SEM: 0.07) episodes/day	NS	No evidence to support contention that BGAT-3 reduces the incidence of hypoglycemia in tightly controlled individuals with type 1 diabetes any more effectively than does a non-specific control.
		Cholesterol Ed.	0.68 (SEM: 0.06) episodes/day		

4.4.6. Section Summary

Our evidence-based conclusions on the effectiveness of hypoglycemia awareness training are presented below.

3. **Awareness training programs (i.e., BGAT and HyPOS) improve the ability of individuals with type 1 diabetes to improve the accuracy in estimating their blood glucose levels (strength of evidence: moderate).**

   A total of six prospective studies that enrolled a total of 334 individuals with type 1 diabetes evaluated the effectiveness of BGAT or a reduced training program called HyPOS in improving the accuracy of self-determined blood glucose estimates. All six studies were controlled; five were randomized controlled trials and one was a non-randomized controlled trial. The overall quality of the evidence base was moderate.

   Qualitative assessment of the available data found that currently available evidence, though not of high quality, consistently demonstrated that BGAT or HyPOS improves the ability of individuals with type 1 diabetes to improve the accuracy of their blood glucose level estimates.

4. **A paucity of consistent evidence precludes a determination from being made concerning whether awareness training (BGAT or HyPOS) is effective in reducing the incidence of severe hypoglycemia.**

Three moderate-quality studies that collectively enrolled a total of 253 individuals with type 1 diabetes presented data on the incidence of severe hypoglycemia following exposure to awareness training. The results of these three small studies were inconsistent, with one study finding a benefit while the other two did not. The inconsistencies in the findings cannot be explained. Given this, it remains unclear whether exposure to awareness training (BGAT or HyPOS) results in measurable reductions in the incidence of severe hypoglycemia among individuals with type 1 diabetes.

Appendix A: Literature Search Approach

Table A1: Key Question 1

Set Number	Concept	Search Statement	Number Retrieved
1	Diabetes/ hypoglycemia	Diabetes OR Hypoglyc*	394,552
2	Accidents	"Accidents, Traffic"[Mesh] or (traffic) or (highway safety) or (motor traffic accident*) or (traffic accident) or (traffic safety) or (crash) or (wreck) or (collision) or (Accidents, Traffic/)	59,795
3	Driving	"Motor Vehicles"[Mesh] or "Automobiles"[Mesh] or "Automobile Driving"[Mesh] or "Motor Vehicles"[Mesh] or (automobile driving*) or (motor vehicle*) or (motor vehicles/) or (motor vehicle/) or (automobiles) or (driving behavior/) or (car driving/) or (driving)	59,025
4	Combine	#2 OR #3	105,605
5	Combine	#1 AND #4	1,143
6	Limit	Humans, English, Publication Date from 2006/01/01 to 2010/11/4	270 * Endnote File

*Search results were imported into Endnote for review.

Table A2: Key Question 2

Set Number	Concept	Search Statement	Number Retrieved
1	Diabetes/ hypoglycemia	Diabetes OR Hypoglyc*	395,315
2	Accidents	"Accidents, Traffic"[Mesh] or (traffic) or (highway safety) or (motor traffic accident*) or (traffic accident) or (traffic safety) or (crash) or (wreck) or (collision) or (Accidents, Traffic/)	59,940
3	Driving	"Motor Vehicles"[Mesh] or "Automobiles"[Mesh] or "Automobile Driving"[Mesh] or "Motor Vehicles"[Mesh] or (automobile driving*) or (motor vehicle*) or (motor vehicles/) or (motor vehicle/) or (automobiles) or (driving behavior/) or (car driving/) or (driving)	59,183
4	Cognition/reaction time/psychological and neuropsychological tests	(Neuropsychological Tests) OR (Cognition) OR (Reaction Time) OR (psychological tests)	457,644
5	Combine	#2 OR #3	105,861
6	Combine	#1 AND #5	1,145
7	Combine	#1 AND #4	5,618
8	Combine & limit	# 6 and #7 Humans, English, Publication Date from 1964/01/01 to 2010/11/16	4,652 * Endnote File

*Search results were imported into Endnote for review.

Table A3: Key Question 3

Set Number	Concept	Search Statement	Number Retrieved
1	Diabetes/ hypoglycemia	Hypoglycemia OR Hypoglycaemia	30,509
2	Risk factors	Risk factors	54,4174
3	Epidemiology	Incidence or prevalence or epidemiology	1,706,800
4	Combine	#2 OR #3	1958084
5	Combine	#1 AND #4	4213
6	Limit	Humans, English, Publication Date from 2000/01/01 to 2010/11/4	2057
7	Limit	Publication Type: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study, Research Support, American Recovery and Reinvestment Act, Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S	1498 * Endnote File
8	Treatment: injectable non-insulin	"exenatide"[Mesh] or "pramlintide"[Mesh] or (AC 2993) or (AC 2993 LAR) or (Byetta) or (Ex4 peptide) or (exendin 4) or (exendin-4) or (AC 0137) or (AC 137) or (pramlintide acetate) or (Symlin) or (Tripro-Amylin)	855 * Endnote File (Deduped with #7)

Table A4: Key Question 4

Set Number	Concept	Search statement	# Retrieved
1	Diabetes/ hypoglycemia	Diabetes OR Hypoglyc*	39,5423
2	BGAT	(Blood glucose awareness training) OR BGAT OR (Hypoglycemia anticipation awareness and treatment training) OR (HAATT) OR (Blood glucose discrimination training) OR (Blood Glucose Self-Monitoring) OR ((patient education as a topic) AND (blood glucose)) OR ((awareness) AND (blood glucose))	5,526
3	Combine	#1 AND #2	4,482
4	Limit	Humans, English, Publication Date from 2006/01/01 to 2010/11/4	1,165
5	Limit	Publication Type: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Review, Comparative Study, Controlled Clinical Trial, Guideline, Multicenter Study, Research Support, American Recovery and Reinvestment Act, Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S,	796

Additional searches included:

- PsycINFO and CINAHL Full text through EBSCO
- TRIS, the Transportation Research Information Services bibliographic database, using a combination of terms related to diabetes, hypoglycemia, traffic accidents, driving, and motor vehicles
- The Cochrane Library for systematic reviews related to diabetes, hypoglycemia, and treatment-related issues

Endnote files were established for each key question and files from varied bibliographic databases were merged. After merging, duplicate references were removed.

Appendix B: Retrieval and Inclusion Review

Key Question 1

Retrieval Criteria

- 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 either directly (risk for a fatal or non-fatal crash) associated with diabetes.
- Article must describe a study that includes a comparison group composed of comparable subjects who do not have diabetes.

Inclusion Criteria

- 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.
- Article must describe a study that attempted to directly determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) associated with diabetes.
- Article must describe a study that includes a comparison group composed of comparable subjects who do not have diabetes.
- 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.

Excluded Articles

Table B1: Key Question 1 Exclusion Table

Reference	Year	Reason for Exclusion
New Evidence 2010 Update		
Cox et al.[14]	2009	No comparison group
Leproust et al.[143]	2007	Case-crossover design (cases were their own controls; risk of motor vehicle crash [MVC] among diabetics was before medical contact was compared with the risk of MVC after medical contact among the same diabetic subjects) No non-diabetics subjects were included in the study.
Marshal[144]	2008	Systematic review Bibliographies were evaluated to ensure nothing was missed from the previous report

Reference	Year	Reason for Exclusion
Redelmeier et al.[145]	2009	All study subjects are diabetic and crash risk was calculated among them
Robb et al.[146]	2008	Systematic review. Bibliographies were examined to ensure nothing was missing from the previous report. Does not address Key Question 1
Sagberg et al.[147]	2006	All subjects were involved in a crash. No data provided for non-diabetics; method (induced-exposure method) does not allow one to determine crash risk of diabetics when compared with rest of population. OR for crash based on data from 16 diabetics at fault for a crash and 8 diabetics involved in a crash but not at fault. Control group too small.
Songer et al.[148]	2006	Study data included in the evidence base of the original report
Evidence from 2006 report		
Harsch et al.[149]	2002	Does not address Key Question 1. Does address Key Question 3.
Songer et al.[150]	2002	Does not address Key Question 1. Presents risk factors for crash among individuals with diabetes.
Kennedy et al.[151]	2002	Does not address Key Question 1. All individuals were involved in an accident that hospitalized the individual for 3 or more days.
Gislason et al.[152]	1997	Does not address Key Question 1. No outcome data relevant to Key Question 1 presented that could be assessed.
MacLeod et al.[16]	1993	Does not address Key Question 1
Mathiesen et al.[153]	1997	Does not address Key Question 1. Examines risk of any type of accident. Does not report motor vehicle crash data separately.
Cox et al.[154]	2005	Abstract only
Cox et al.[155]	2004	Abstract only
Dionne et al.[156]	1993	Superseded by more recent article
Diamond et al.[157]	2005	5 selected case reports
Canfield et al.[158]	2000	Does not address Key Question 1. Aircraft crashes
Waller[159]	1968	Does not address Key Question 1. Crash data for individuals with diabetes not presented. separately
Frais et al.[160]	1972	Letter
Christian et al.[161]	1972	Letter
Leyshon et al.[162]	1972	Case report
Santer et al.[163]	1972	Letter
Clarke et al.[21]	1980	Letter
Kernbach-Wighton et al.[164]	2003	Does not address Key Question 1. Hypoglycemia and moving violations
Dionne et al.[165]	1995	Superseded by more recent article

Key Question 2

Retrieval Criteria

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article may describe a study that attempted to evaluate the relationship between hypoglycemia and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must describe a study that includes a comparison group composed of comparable individuals with diabetes who did not have hypoglycemia at the time of testing.

Inclusion Criteria

- 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.
- Article may describe a study that attempted to evaluate the relationship between hypoglycemia and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must describe a study that includes a comparison group composed of comparable individuals with diabetes who did not have hypoglycemia at time of testing, OR
- **NEW in 2010**: Article must describe a study that employed a self-controlled study design (where individuals served as their own control, with testing performed in the euglycemic state and the induced hypoglycemic state)

Excluded Articles

Table B2: Key Question 2 Exclusion Table

Reference	Year	Reason for Exclusion
Juhl et al.[166]	2010	No outcome of interest to key question addressed
de Galan et al.[167]	2009	No outcome of interest to key question addressed
Hoi-Hansen et al.[168]	2009	No outcome of interest to key question addressed
Smeeton et al.[169]	2009	No outcome of interest to key question addressed

Reference	Year	Reason for Exclusion
Rossetti et al.[170]	2008	No outcome of interest to key question addressed
Brismar et al.[171]	2007	Includes subjects with diabetic retinopathy and other complications
Warren et al.[172]	2007	No outcome of interest to key question addressed
McAulay et al.[73]	2006	Includes same subjects from another study meeting inclusion criteria
Schultes et al.[173]	2005	Examines effects of hypoglycemia in individuals without diabetes
Zammitt et al.[174]	2005	Abstract
Brody et al.[175]	2004	Examines effects of hypoglycemia in individuals without diabetes
Ferguson et al.[176]	2003	Testing was not performed during hypoglycemia
Cox et al.[77]	2003	Case-control study using evidence base included in Cox et al.[23]
Hermanns et al.[177]	2003	No outcome of interest to key question addressed
Schachinger et al.[178]	2003	Examines effects of hypoglycemia in individuals without diabetes
Stork et al.[179]	2003	Abstract
Fanelli et al.[180]	2002	Not a research study
Heller et al.[181]	2002	No outcome of interest to key question addressed
McAulay et al.[182]	2001	Examines effects of hypoglycemia in individuals without diabetes
Owen et al.[183]	2001	Examines effects of hypoglycemia in individuals without diabetes
Howorka et al.[184]	2000	Testing was not performed during hypoglycemia
Strachan et al.[185]	2000	No outcome of interest to key question addressed
Taverna et al.[186]	2000	No outcome of interest to key question addressed
Evans et al. [187]	2000	Examines effects of hypoglycemia in individuals without diabetes
Fruewald-Schultes et al.[188]	2000	Examines effects of hypoglycemia in individuals without diabetes
Austin et al.[189]	1999	Included subjects outside the age range
McCrimmon et al.[190]	1999	No outcome of interest to key question addressed
Fanelli et al.[75]	1998	No abstract
Kramer et al.[191]	1998	Patients with retinopathy not excluded
Jones et al.[192]	1997	No outcome of interest to key question addressed
McCrimmon et al.[193]	1997	No outcome of interest to key question addressed
DCCT study[194]	1996	Included subjects outside the age range
Howorka et al.[195]	1996	No outcome of interest to key question addressed
Lincoln et al.[196]	1996	No outcome of interest to key question addressed
McCrimmon et al.[197]	1996	Examines effects of hypoglycemia in individuals without diabetes
Fitten et al.[198]	1995	Not relevant

Reference	Year	Reason for Exclusion
Gold et al.[199]	1995	Examines effects of hypoglycemia in individuals without diabetes
Ryan et al.[200]	1993	No testing done during hypoglycemia
Sachon et al.[201]	1992	No testing done during hypoglycemia
Langan et al.[202]	1991	Patients with retinopathy and nephropathy not excluded
Blackman et al.[203]	1990	Examines effects of hypoglycemia in individuals without diabetes
Stevens et al.[204]	1989	Examines effects of hypoglycemia in individuals without diabetes
Holmes et al.[205]	1988	Compared groups of diabetics with normal control or poor control. <10 patients per arm.
Hung et al.[206]	1984	No outcome of interest to key question addressed

Key Question 3

NOTE: No inclusion/exclusion criteria were applied. A qualitative summary of available studies was summarized for this key question. Because of the breadth of material available in the medical literature pertaining to this question, we focused our examination of the literature on systematic evidence reviews and meta-analyses relevant to the key question.

Key Question 4

Retrieval Criteria

- 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 evaluate the effectiveness of hypoglycemia awareness training.
- Article should describe a controlled trial.

Inclusion Criteria

- Article must describe a study that attempted to evaluate the effectiveness of hypoglycemia awareness training.
- Article must describe a study that utilized a control group composed of comparable individuals who did not receive hypoglycemia awareness training or,
- Article must describe a study that compared effectiveness of hypoglycemia awareness training in groups of individuals who differed from one another in their blood glucose awareness status.
- 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.

Excluded Articles

Table B3: Key Question 4 Exclusion Table

Reference	Year	Reason for Exclusion
Plack et al.[207]	2010	Does not address Key Question 4. Not a hypoglycemic awareness training (HAT) study
Amsberg et al.[208]	2009	Does not address Key Question 4. Not HAT study
Amsberg et al.[209]	2009	Does not address Key Question 4. Not HAT study
Cox et al.[133]	2008	Relevant, but no control group. Discussed in background for Key Questions 4
Heller et al.[210]	2008	Does not address Key Question 4. Not HAT study
Snoek et al.[211]	2008	Does not address Key Question 4. Not HAT study
Stork et al.[26]	2007	Does not address Key Question 4. Not HAT study
Wild et al.[212]	2007	Does not address Key Question 4. Not HAT study
Fehm-Wolsdorf et al.[213]	2005	Meeting abstract
Grossman et al.[214]	2005	Case reports
Nordfeld et al.[215]	2005	Does not address Key Question 4. HAT study
Van der Ven[216]	2005	Does not address Key Question 4. Not HAT study
Hernandez et al.[217]	2004	Does not address Key Question 4. Not HAT study
Nebel et al.[218]	2004	Does not address Key Question 4. Not HAT study
Braun et al.[219]	2004	Does not address Key Question 4. Not HAT study
Erskine et al.[220]	2003	Does not address Key Question 4. Not HAT study
DAFNE Study Group[221]	2003	Does not address Key Question 4. Not HAT study
Nordfeld et al.[222]	2003	Does not address Key Question 4. Not HAT study
Cox et al.[223]	2001	No control group
Cox et al.[224]	2001	Meeting abstract
Snoek et al.[225]	2001	Does not address Key Question 4. Not HAT study
Tankova et al.[226]	2001	Does not address Key Question 4. Not HAT study
Bott et al.[227]	2000	Does not address Key Question 4. Not HAT study
Schiel et al.[228]	1998	Does not address Key Question 4. Not HAT study
Schiel et al.[229]	1997	Does not address Key Question 4. Not HAT study
Cox et al.[230]	1995	No control group
Fanelli et al.[231]	1994	Does not address Key Question 4. Not HAT study

Reference	Year	Reason for Exclusion
Nurick et al.[232]	1991	Study size too small

Appendix C: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic review in that we provide two types of conclusion; 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. The algorithm, which is presented in Figure C-3 through Figure C-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 to 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) guides 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 composed 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; 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 non-randomized 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). These instruments are presented in Appendix D.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key-question-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 C-1.

Table C-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EQS I Score	Median EQS III Score	Median NOQAS Score
High quality	≥8.0		
Moderate quality	6.0 to 7.9	≥9.0	≥8.0
Low quality	≤6.0	<9.0	<8.0

Note that it is not possible for an evidence base consisting of case-control trials to be categorized as high quality. This is the consequence of the fact that this study design can never be protected from potential bias.

Decision Point 3: Quantitative Analysis Performed?

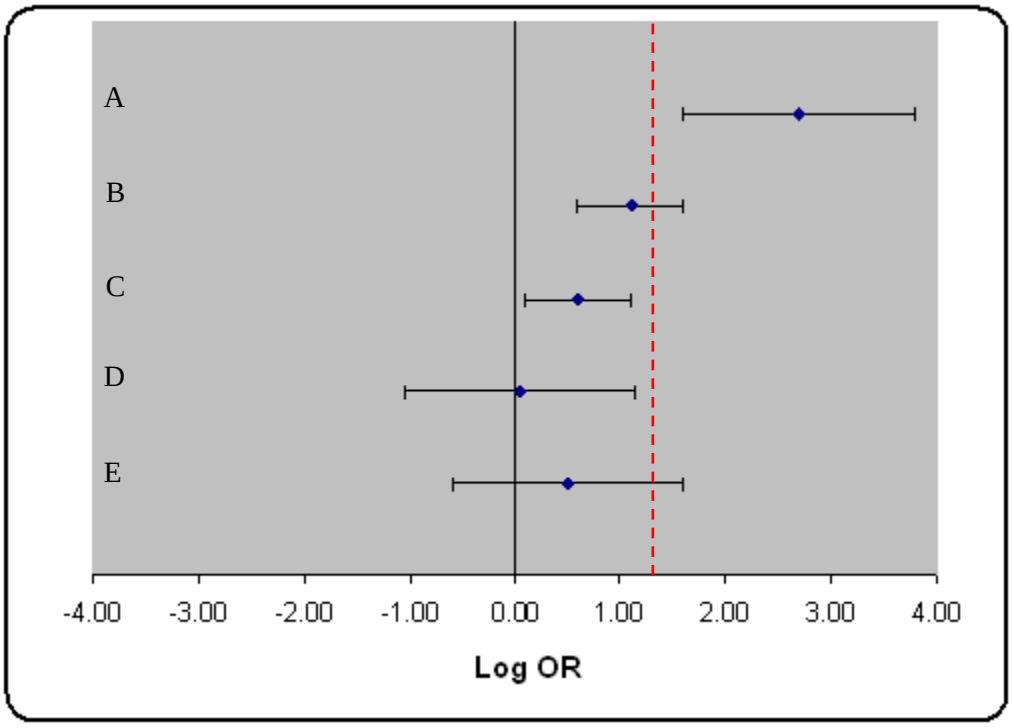
In this evidence report, the answer to Decision Point 3 depended on a number of factors; the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least three studies must be available before a quantitative analysis will be considered. If four 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.(7) 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 fixed-effects meta-analysis (FEMA). Having obtained a summary effect-size estimate, we then determined whether this estimate 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 C-1. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure C-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 non-informative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis 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 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 are:

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

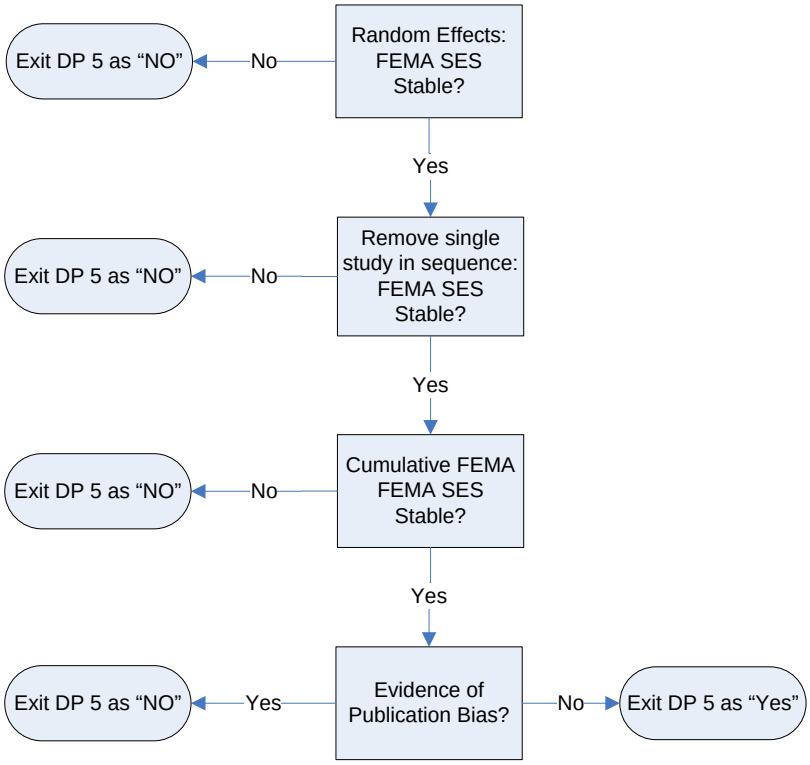
includes imprecise estimates of treatment effect calculated for all available studies will be performed. For this evidence report, the summary estimate of treatment effect determined by this analysis will be compared with the summary effect-size estimate determined by the original fixed-effects meta-analysis. If the random-effects effect-size estimate differs from the original fixed-effects meta-analysis by >±5%, the original effect-size estimate will not be considered stable.

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[49-52]. Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test[12,13] estimates the number of unpublished studies (and their effect sizes). After 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 fixed-effects meta-analysis 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 fixed-effects meta-analysis.* 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 fixed-effects meta-analyses:
    a. Studies were added in order of weight.
    b. Studies were added cumulatively to a fixed-effects meta-analysis by date of publication, oldest study first.
    c. Studies were added cumulatively to a fixed-effects meta-analysis by date, 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 base (100% or <100% ≥75% of total available evidence base), two slightly different sets of sensitivity analyses are needed. Figure C-2 shows the procedural algorithm that was used when dealing with these two types of evidence base.

Figure C-2. Sensitivity Analysis Algorithm 1: Used when Original Fixed-Effects Meta-Analysis 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 non-significant 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

with 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 one's qualitative conclusion.

The algorithm divides the magnitude of effect into two categories – large and not large. Determining the threshold above at 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 C-3. General Section

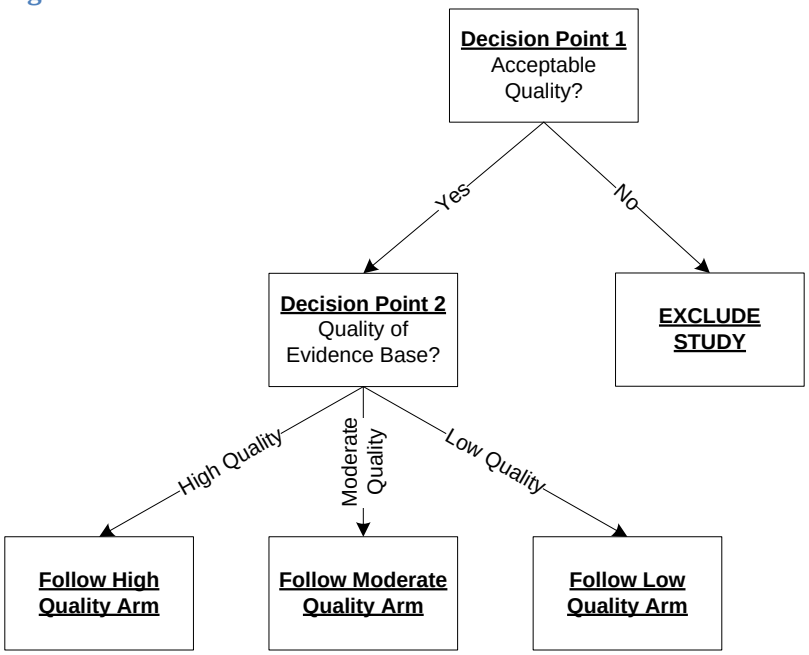


Figure C-4. High-Quality Pathway

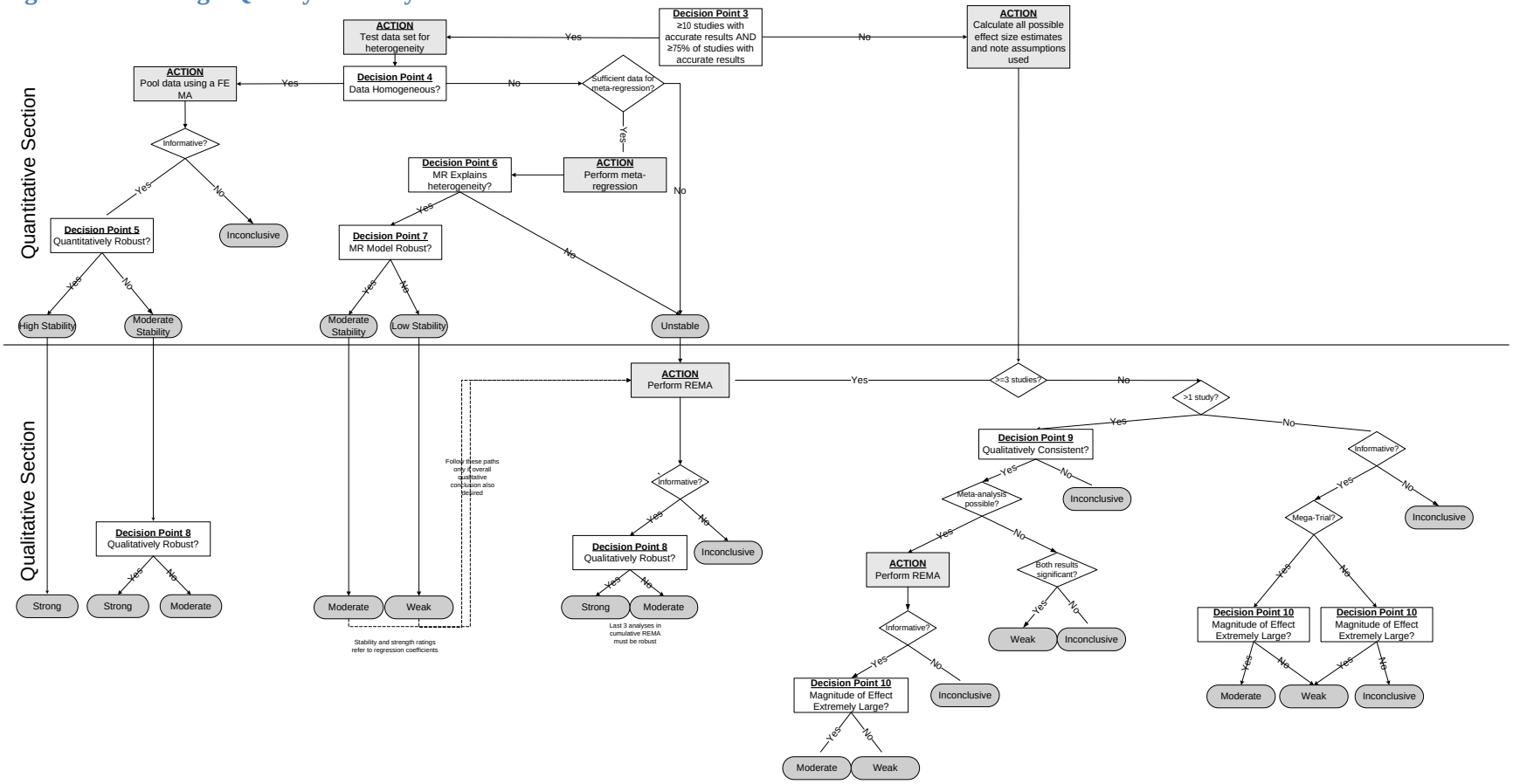


Figure C-5. Moderate-Quality Pathway

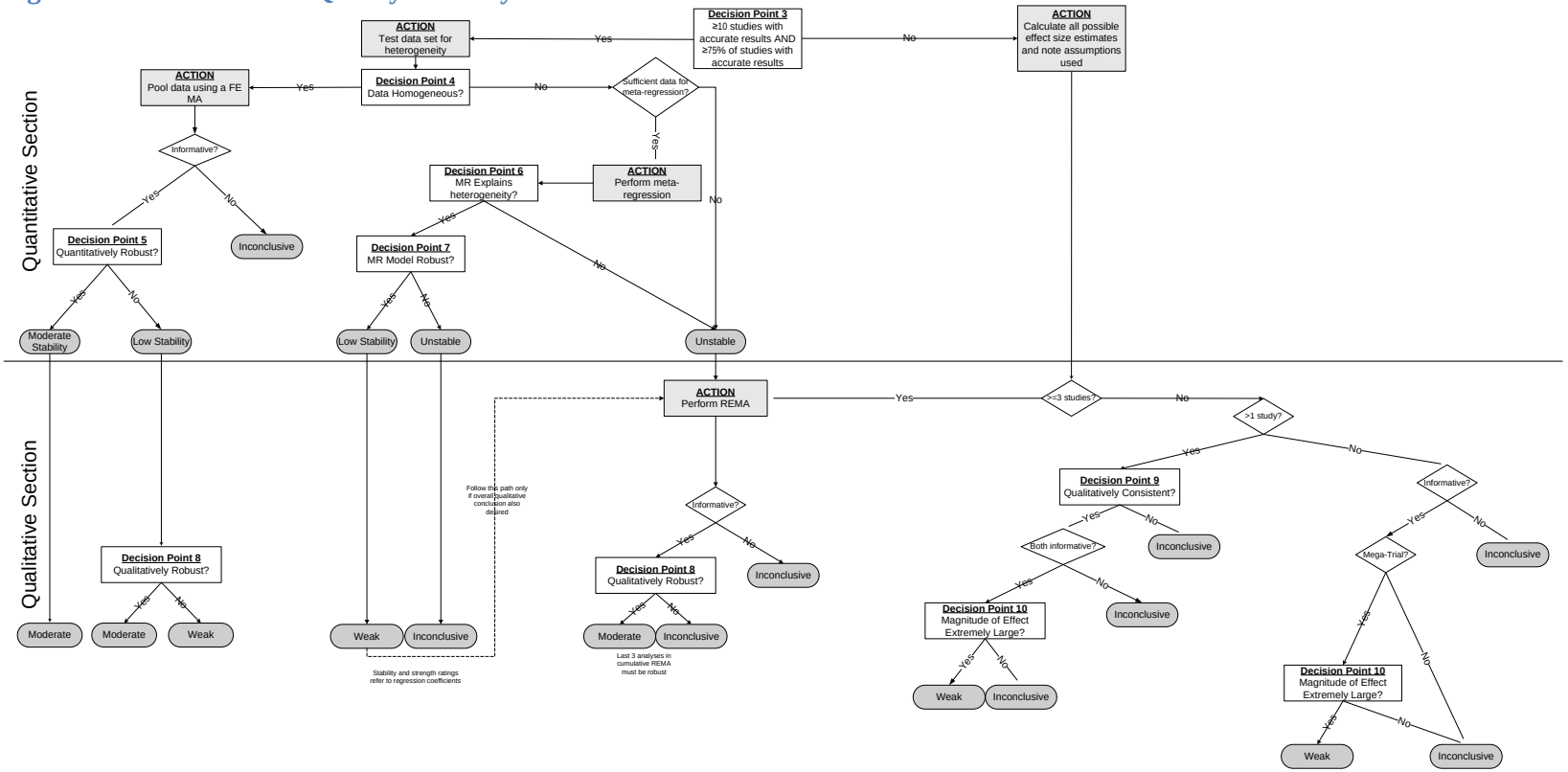
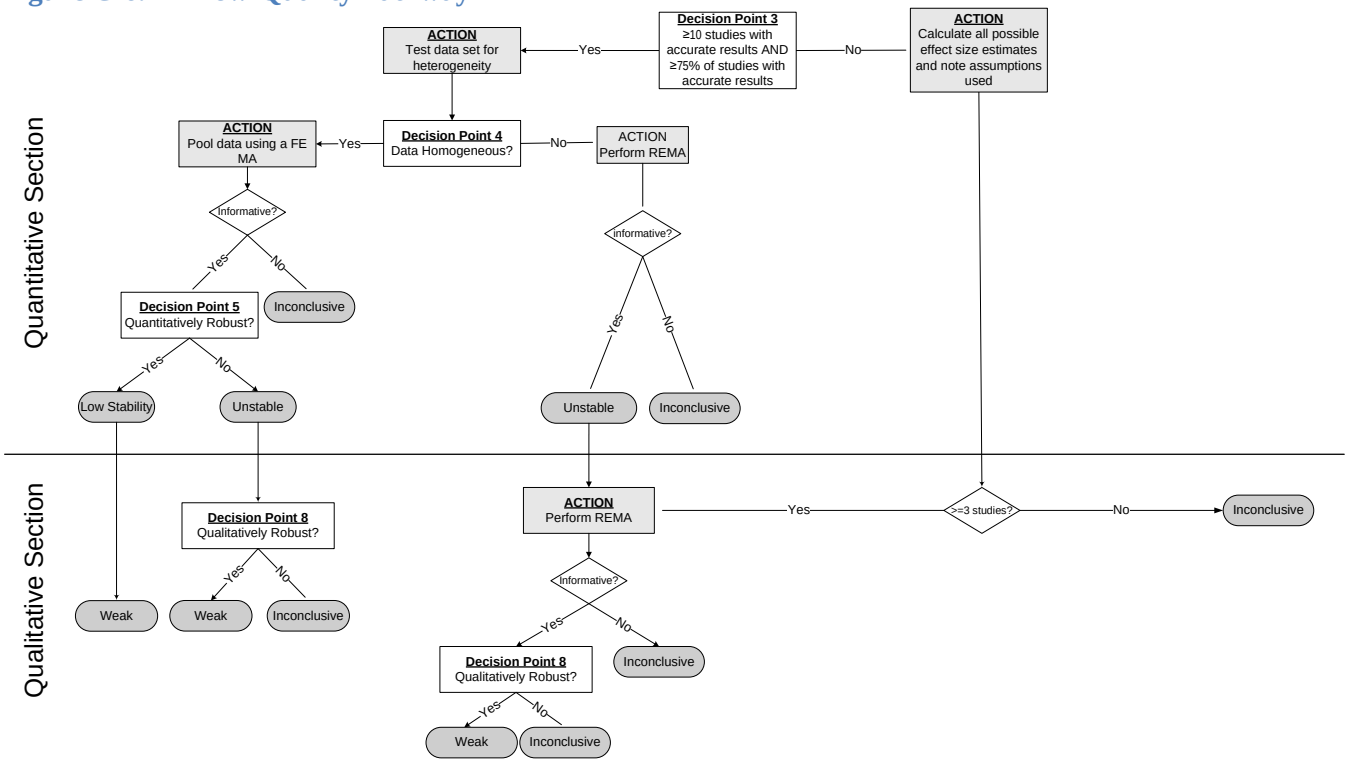


Figure C-6. Low-Quality Pathway



Appendix D: 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.[233]

ECRI Quality Scale I: Controlled Trials

Domain	Question #	Question
Comparability	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?
Blinding	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 patients' outcomes blinded to the group to which the patients were assigned?
	17	Was there concealment of allocation?
Outcomes	18	Was the outcome measure of interest objective and was it objectively measured?
	19	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
	20	Was the instrument used to measure the outcome standard?
Intervention	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?
Investigator bias	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,

Domain	Question #	Question
		supported by the data presented in the article's results section?

ECRI Quality Scale III: Pre-Post Studies

Domain	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 was it 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?
Investigator bias	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?

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.

Domain	Question #	Question
Selection	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?
Comparability	5	Does the study control for the most important confounder?
	6	Does the study control for any additional confounders?
Exposure/Outcome	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 non-response rate of both groups the same?
	11	Was the investigation time of the study the same for both groups?

Domain	Question #	Question
Investigator bias	12	Was the funding free of financial interest?
	13	Were the conclusions supported by the data?

Appendix F: Diabetes-Related Standards and Guidelines – International Comparison

Country	United States (2009)
Source	http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.aspx?chunkKey=09016334800238b9
STANDARD	§ 391.41 Physical qualifications for drivers. (b)(8) A person is physically qualified to drive a commercial motor vehicle if that person: (b)(3) Has no established medical history or clinical diagnosis of diabetes mellitus currently requiring insulin for control;
Medical advisory criteria	Diabetes mellitus is a disease which, on occasion, can result in a loss of consciousness or disorientation in time and space. Individuals who require insulin for control have conditions which can get out of control by the use of too much or too little insulin, or food intake not consistent with the insulin dosage. Incapacitation may occur from symptoms of hyperglycemic or hypoglycemic reactions (drowsiness, semi-consciousness, diabetic coma, or insulin shock). The administration of insulin is within itself, a complicated process requiring insulin, syringe, needle, alcohol sponge and a sterile technique. Factors related to long-haul commercial motor vehicle operations such as fatigue, lack of sleep, poor diet, emotional conditions, stress, and concomitant illness, compound the diabetic problem. Because of these inherent dangers, the FMCSA has consistently held that a diabetic who uses insulin for control does not meet the minimum physical requirements of the FMCSR. Hypoglycemic drugs, taken orally, are sometimes prescribed for diabetic individuals to help stimulate natural body production of insulin. If the condition can be controlled by the use of oral medication and diet, then an individual may be qualified under the present rule. See Conference Report on Diabetic Disorders and Commercial Drivers and Insulin-Using Commercial Motor Vehicle Drivers at: http://www.fmcsa.dot.gov/rulesregs/medreports.htm Diabetes Exemption Program Criteria available at: http://www.fmcsa.dot.gov/documents/safetyprograms/Diabetes/diabetes-exemption-package0706.pdf
Country	Australia, *Accessing Fitness to Drive; Austroads Inc. 2003 (reprinted 2006)*
Source	http://austroads.com.au/aftd/downloads/AFTD_text_08-2006.pdf
STANDARD	5.3 MEDICAL STANDARDS FOR COMMERCIAL LICENSING (Drivers of heavy vehicles, public passenger vehicles or bulk dangerous goods vehicles – refer to definition, page 6 of the standards document). 5.3.1 Medical criteria for unconditional and conditional licenses are outlined below. 5.3.2 For diabetes-related end organ damage, for example diabetic retinopathy, see the appropriate chapter. In the case of commercial vehicle drivers, the opinion of a medical specialist is required for recommendation of a conditional license. This requirement reflects the higher safety risk for commercial vehicle drivers and the consequent importance of expert opinion. In rural or remote areas, however, where access to specialists may be difficult, the Driver Licensing Authority may agree to a process in which: • Initial assessment and recommendation for the conditional license is provided by a specialist; • Ongoing periodic review for the conditional license is provided by the treating GP, with the approval of the specialist. Diabetes controlled by diet alone A person with diabetes controlled by diet alone may drive without license restriction and without notification to the Driver Licensing Authority. They should be reviewed by their treating doctor periodically regarding progression of the illness.

	Non-Insulin Requiring Type 2 Diabetes Mellitus The criteria for an unconditional license are NOT met: • If the person has non-insulin requiring diabetes mellitus on oral hypoglycemic agents. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a specialist in Diabetes or Endocrinology, and the nature of the driving task, and subject to at least annual review: • If the condition is well controlled and the patient compliant with treatment; and • There is an absence of defined hypoglycemic episodes as assessed by the specialist, the patient has awareness (sensation) of hypoglycemia, and the patient is taking agents that provide the minimum risk of hypoglycemia; and • There is an absence of end organ effects which may affect driving as per this publication. Insulin-Requiring Diabetes Mellitus (both Types 1 and 2) The criteria for an unconditional license are NOT met: • If the person has Insulin Requiring Diabetes Mellitus. A conditional license may be granted by the Driver Licensing Authority, taking into account the opinion of a specialist in Diabetes or Endocrinology, and the nature of the driving task, and subject to at least annual review: • If the condition is well controlled and the patient compliant with treatment; and • There is an absence of defined hypoglycemic episodes as assessed by the specialist, the patient has awareness (sensation) of hypoglycemia, and the patient is taking agents that provide the minimum risk of hypoglycemia; and • There is an absence of end organ effects which may affect driving as per this publication. In the event of a defined hypoglycemic episode occurring in a previously well-controlled person they should not drive for a period determined by a specialist. In the event of a defined hypoglycemic episode being associated with a motor vehicle crash the Driver Licensing Authority must be notified.
Additional guidance	5.1 RELEVANCE TO DRIVING TASK 5.1.1 Diabetes may affect a person's ability to drive, either through loss of consciousness in a hypoglycemic episode or from end organ effects on relevant functions, including effects on vision, the heart, the peripheral nerves and vasculature of the extremities, particularly the feet. The main hazard in people with insulin-requiring diabetes is the unexpected occurrence of hypoglycemia. 5.2 HYPOGLYCEMIA 5.2.1 A "defined" hypoglycemic event relevant to driving is one of sufficient severity to cause impairment of perception or motor skills, abnormal behavior or impairment of consciousness. It is to be distinguished from mild hypoglycemic symptoms such as sweating, tremulousness, hunger, tingling around the mouth, etc., which are common occurrences in the life of a person with diabetes treated with insulin and some hypoglycemic agents. 5.2.2 Hypoglycemia may be caused by many factors, including non-compliance or alteration to medication, unexpected exertion or irregular meals. Irregular meals may be an important consideration with long-distance commercial driving or those operating on shifts. Impairment of consciousness and judgment may develop rapidly and result in the loss of control of a vehicle. 5.2.3 The driver should be advised not to drive after a defined hypoglycemic episode or after a hypoglycemic episode experienced while driving until they have been cleared by the primary care physician or specialist. 1.2.4 The driver should also be advised to take appropriate precautionary steps to avoid hypoglycemic episodes, for example: • Self-monitoring of blood glucose levels; • Carrying of glucose in the vehicle; • Compliance with specified review periods (GP or specialist); and • Cessation of driving should a hypoglycemic episode occur.

License classification	The medical guidelines outline two sets of medical standards – private vehicle driver standards and commercial vehicle driver standards. Private standards • Drivers applying for or holding a license class C (Car), R (Motorcycle) or LR (Light Rigid) UNLESS the driver is also applying for an authority or is already authorized to use the vehicle for carrying public passengers for hire or reward or for the carriage of bulk dangerous goods or in some jurisdictions for a driver instructor's license. Commercial standards • Drivers of "heavy vehicles," i.e., those holding or applying for a license of class MR (Medium Rigid), HR (Heavy Rigid), HC (Heavy Combination) or MC (Multiple Combination, refer Table 1). • Drivers applying for an authority/already authorized to carry public passengers for hire or reward (bus drivers, taxi drivers, chauffeurs, drivers of hire cars and small buses, etc.). • Drivers applying for an authority/already authorized to carry bulk dangerous goods.
Country	Canada, *Canadian Council of Motor Transport Administrators* (*CCMTA) Medical Standards for Drivers (June 2009)*
Source	http://www.ccmta.ca/english/pdf/medical_standards_march_2009.pdf
STANDARD	8.2 Diabetes Mellitus Diet control • Eligible for any class of license if there are no other disqualifying complications. Oral medication • Eligible for any class of license if there are no other disqualifying complications and not subject to hypoglycemia. • Class 1,2,3,4: annual medical review Insulin-treated Eligible for class 5 license if there are no other disqualifying complications and not subject to hypoglycemia. May be considered for class 1,2,3,4 only if the following conditions are met: 1) No episode of hypoglycemia requiring the need for intervention by an outsider for correction within the previous 2 years; 2) No evidence of hypoglycemia unawareness; 3) The diabetes is well controlled: o The glycosylated hemoglobin is <2.0 times the upper limit of normal, o Less than 10% of blood glucose levels are < 4 mmol/l; 4) Self-monitoring is adequate – a verifiable glycemic log is maintained; 5) Knowledge of the disease and the causes, symptoms and treatment of hypoglycemia is adequate; 6) No other disqualifying complications; 7) Observes the guidelines for driving recommended by the Canadian Diabetes Association dated June 1991; 8) Annual medical review including a complete eye examination including a dilated retinal examination. In the presence of retinopathy, an examination by an ophthalmologist is required. 8.3 Hypoglycemia Individuals subject to spontaneous attacks may not operate any type of motor vehicle until the condition is treated and the cause eliminated. 8.5 Pituitary Diseases Diabetes Insipidus – individual is eligible to operate a Class 5 or 6 motor vehicle based on conditions listed above.
Additional	METABOLIC DISEASES

guidance	8.1 Metabolic Diseases and Driving Disturbances in the endocrine system can cause many symptoms, ranging in severity from muscle weakness and spasm to sudden episodes of dizziness or loss of consciousness. In general, patients with endocrine disorders should not be allowed to drive any type of motor vehicle until the symptoms have been controlled by treatment. (CMA 7) 8.2 Diabetes Mellitus Individuals with diabetes mellitus are at risk for the development of neurological, cardiovascular and ophthalmologic complications, which may interfere with driving ability. In these areas, diabetic individuals must meet the same standards as all other drivers. The major concern in diabetes and driving is hypoglycemia, particularly if there is a lack of awareness of warning symptoms. Type II diabetics treated with insulin are less prone to hypoglycemia because they are relatively resistant to insulin. Hypoglycemia unawareness occurs in individuals with autonomic neuropathy which tends to occur after 10 years in Type I diabetics and after a somewhat longer time in Type II diabetics. Diabetics treated with injectable insulin, who also are on Beta adrenergic blocking agents, may also be at risk for hypoglycemia unawareness because they may not have a sympathetic nervous system response to mild hypoglycemia. In recent years there have been many advances in the treatment of diabetes resulting in tighter control in many individuals. An unavoidable byproduct of tight control is an increased incidence of hypoglycemia, the complication which presents the greatest risk to road users. This risk is reduced if the diabetic driver is well educated, understands the relationship between insulin dose, diet and exercise, and is compliant with treatment. Furthermore, knowledge of the symptoms and treatment of hypoglycemia is essential. Individuals with diabetes treated with diet alone can be considered for any class of license. The same applies to those treated with oral medication provided they are not subject to hypoglycemia and meet the other conditions described above. Diabetics individuals treated with injectable insulin are eligible for a Class 5 license if they are not subject to hypoglycemia and do not have disqualifying cardiovascular, neurologic or ophthalmologic disease. Diabetic individuals treated with injectable insulin are prohibited from holding Class 1 to 4 licenses unless the specific standards which have been recommended by the Canadian Diabetes Association and published in the June 1991 issue of the Canadian Diabetes Association journal are satisfied. The Canadian Diabetes Association has recommended that diabetics treated with injectable insulin who hold commercial licenses observe the following guidelines for driving: 1) The driver must at all times while driving carry self-monitoring equipment, a source of rapidly absorbable glucose on his person, and insulin and syringes/pump/injector; 2) The blood glucose concentration must be tested within an hour before driving and every 4 hours while driving. Driving must be stopped if the blood glucose value is less than 6 mmol/l, until the glucose value has risen by food ingestion; 3) Driving should be limited to a maximum period of 12 hours in a day, with a maximum of 6 consecutive hours between meals. The schedule of work to be adopted should be approved by the treating physician as compatible with the insulin regimen. 8.3 Hypoglycemia Individuals who become faint or unconscious from spontaneous attacks of hypoglycemia cannot drive any type of motor vehicle safely. 8.5 Pituitary Diseases (a) Posterior Deficiency: Individuals with diabetes insipidus may operate Class 5 or 6 motor vehicles, provided the underlying pathology is recognized and treated and visual disturbances or other disabling central nervous symptoms are not present.
License classification	• Class 1: Permits the operation of a motor vehicle of any type or size, with or without passengers, and a trailer of any size. • Class 2: Permits the operation of a motor vehicle of any type or size, with or without passengers. A Class 2 license does not permit the holder to pull a semi-trailer. • Class 3: Permits the operation of a motor vehicle of any size. A Class 3 license does not permit the holder to carry passengers or to pull a semi-trailer. • Class 4: Permits the operation of a taxicab, a bus carrying no more than 24 passengers and emergency response vehicles, such as ambulances, fire trucks and police cars. • Class 5: Permits the operation of any motor vehicle or small truck (a towed vehicle cannot exceed 4,600 kg). A Class 5 license does not permit the holder to drive an ambulance, a taxicab or a bus or to pull a semi-trailer. • Class 6: Permits the operation of a motorcycle, motor scooter or mini-bike only. All other classes must be endorsed to include Class 6 before the holder may operate a motorcycle, motor scooter or mini-bike.

Country	New Zealand, *Medical aspects of fitness to drive. A guide for Medical Practitioners, Land Transport Safety Authority (2009)*
Source	http://www.nzta.govt.nz/resources/medical-aspects/
STANDARD	4. DIABETES 4.1 Type 1 diabetes When driving should cease People with type 1 diabetes are generally considered unfit to drive. When driving may resume or may occur The Agency may, in exceptional circumstances, grant a license, after consultation with the individual's general practitioner and diabetes specialist. Strict conditions are likely to be imposed, which would include the requirements listed below in Section 4.4. 4.2 Type 2 diabetes controlled by diet alone Considered fit for all types of driver's license. 4.3 Type 2 diabetes controlled by oral hypoglycemic Agents These drivers may be considered fit to drive in most circumstances on a license with conditions, provided there is no history of hypoglycemia. An initial review from a diabetes specialist may be required to ensure that the treatment regimen is satisfactory, adequate glycemic control is being achieved and there are no complications of diabetes that may impair driving performance. The granting of a license in these categories is likely to require the following conditions: 1. An annual medical certificate from a GP documenting: Adherence to treatment o That the medical practitioner has proof of regular self-testing of blood glucose with satisfactory blood glucose levels o The absence of hypoglycemic episodes or unawareness o The absence of significant diabetic complications 2. A regular pattern of shifts with adequate meal breaks 3. A satisfactory two-yearly specialist assessment. If the addition of insulin is required to achieve better glycemic control, then the individual should be considered under section 4.4. 4.4 Type 2 diabetes partly or solely controlled by insulin In cases where insulin has been added to the treatment, additional conditions are likely to be imposed, and not all individuals will necessarily be considered fit to drive. Nocturnal insulin therapy, when clinically appropriate, carries a lower risk of daytime hypoglycemia than twice daily or morning insulin regimens, especially those with short-acting components. A review from a diabetes specialist is necessary to ensure that the treatment regimen is satisfactory, adequate glycaemic control is being achieved and that there are no complications of diabetes that may impair driving performance. The granting of a license in these categories is likely to require the following conditions: 1. A six monthly medical certificate from a GP documenting: o Adherence to treatment o That the medical practitioner has proof of regular self-testing of blood glucose with satisfactory blood glucose levels o The absence of hypoglycemic episodes or unawareness, and o The absence of significant diabetic complications. 2, A regular pattern of shifts with adequate meal breaks 3. A satisfactory annual specialist review.
Additional guidance	INTRODUCTION OF STANDARDS Diabetes is a common condition in New Zealand. Current estimates suggest that at least 100,000 people are being treated for the condition and many more are as yet undiagnosed (Ministry of Health 2008). The number of road traffic crashes attributable to diabetes or its treatment is not known, but it is likely to be relatively small. Monitoring by the Agency suggests that diabetes accounts for about 5–10 percent of those motor vehicle crashes attributable to medical factors. The potential risks of diabetes derive from the metabolic disturbances associated with control of blood glucose on the one hand, and the later complications of the disease on the

	other. The later complications, giving rise to end organ damage, should be assessed separately using advice from the appropriate sections of this guide. Specifically, these include: • Visual acuity problems arising from cataract formation and/or diabetic retinopathy and its treatment (Section 6). (Note that subjects who have had extensive laser photocoagulation of the retinae often have very poor vision at night, despite adequate daytime acuity, and may also have visual field limitation.) • Ischemic heart disease and cerebrovascular disease, both of which are more prevalent in people with diabetes (Sections 3 and 2, respectively). • Locomotor conditions, particularly of the lower limbs, arising from peripheral neuropathy and/or peripheral vascular disease (Section 5). Note: Obstructive sleep apnea is not uncommon in obese subjects with type 2 diabetes (Section 10). Hyperglycemia and associated diabetic coma (whether ketotic or nonketotic) are generally of little significance to driver safety, as the onset is slow. Hypoglycemia induced by treatment of diabetes is undoubtedly the most important potential problem from the point of view of driving safety. Its onset may rapidly impair the ability of an otherwise competent and safe driver. It may result in poor motor coordination, impaired judgment and reaction times, inappropriate and aggressive behavior, and even loss of consciousness. These all pose a potential risk on the roads. The risk of hypoglycemia is not the same in all patients with diabetes, and the forms of treatment associated with different types of the disease are given different weightings in the guidelines that follow. The risks of hypoglycemia are greater with increased driving hours, and the consequences of an accident are potentially greater with larger vehicles and those carrying passengers. Higher safety standards are therefore required for these classes and endorsements. Hypoglycemia — causes Hypoglycemia is a side effect of treatment of diabetes with insulin or sulphonylurea drugs and also with some newer drugs not currently available in New Zealand. The risk of hypoglycemia with sulphonylurea drugs is greatest in the elderly, and in subjects with weight loss and poor renal function. It is most likely to occur with long-acting agents, such as glibenclamide. In insulin users hypoglycemia usually arises through missed meals, inaccurate or inappropriate insulin dosing, and during or following exercise. It is common in those attempting or achieving tight glycaemic control. With either sulphonylurea drugs or insulin, hypoglycemia can also occur with alcohol consumption. Hypoglycemia unawareness An inability to detect developing hypoglycemia and to respond to it appropriately in good time is the single greatest hazard for diabetic drivers. The risk of crashing may be increased twenty-fold in this group (Lave et al, 1993). As with alcohol intoxication, individuals with this problem may significantly underestimate the degree to which their driving is impaired. The major risk factors for hypoglycemia unawareness are: • A prior history of severe hypoglycemia • intensive hypoglycemic therapy • Type 1 diabetes of long duration In this context severe hypoglycemia is defined as that requiring the help of another party to manage it. Important questions for practitioners to ask in the detection of hypoglycemia unawareness are: 1. *Have you recently experienced severe hypoglycemia?* and *How many episodes have there been in the last 12 months?* Daytime and night time (waking from sleep) episodes should be documented separately. 2. W*hat symptoms tell you that your blood glucose is getting low?* Individuals who report sweating, shaking, tremor and palpitations as their early warning symptoms are likely to have adequate awareness. Those who report confusion, slurred speech, unsteadiness, difficulty concentrating and sleepiness are likely to have impaired awareness. 3. *Are you usually able to detect hypoglycemia before your partner (or friends, family or colleagues)? Or are they usually the first to realize that you are"hypo" and draw your attention to it? (The latter suggests unawareness.)* Corroboration by a partner, family member, friend or colleague strengthens the conclusions that can be drawn from the individual's answer. Inspection of the individual's home blood glucose recordings is important. Individuals with hypoglycemia unawareness often have levels of 3mmol/l or less without symptoms. Those with more than 5-10 percent of readings below 4mmol/l are also likely to be at risk. HbA1c measurements are often close to, or in, the normal range in such individuals. Hypoglycemia unawareness is an indication for specialist referral. It can be difficult to manage successfully. The basis of management involves some relaxation of glycaemic targets, intensive self blood glucose monitoring to detect periods of unrecognized hypoglycemia (particularly at night) and the modification of meals and the insulin regimen. Individuals with very marked hypoglycemia unawareness, usually those with type 1 diabetes, should not drive until their condition can be successfully managed, if this is

	possible. If hypoglycemia unawareness has been successfully managed, an appropriate observation period free of episodes should be required before allowing a return to driving. A specialist assessment should be undertaken before a return to driving. Management of hypoglycemia People taking either insulin or sulphonylurea drugs should be made aware of the precautions they should take to avoid hypoglycemia whilst driving, and to manage it should it occur. Adequate education, by an experienced diabetes nurse educator, is strongly recommended for these individuals. These precautions, which apply to all such individuals whatever their class of license/endorsement, include: • Regular testing and recording of blood glucose, especially before driving • Testing blood glucose every couple of hours on long journeys • Always carrying a form of rapidly absorbed glucose within easy reach in the vehicle • Always having a meal or snack before undertaking long journeys • Telling co-travelers that the individual has diabetes The action to be taken if hypoglycemia does occur whilst driving includes: • Stop the car and eat fast-acting sugary food • Eat a meal of longer lasting carbohydrate as soon as possible • Wait until recovery is complete before resuming the journey Alcohol Alcohol use is particularly hazardous for drivers with diabetes. As well as impairing driving performance in its own right, alcohol can precipitate hypoglycemia (if food intake is inadequate) and it increases hypoglycemia unawareness. Temporary unfitness to drive Following mild hypoglycemia, individuals should not drive for at least an hour, as full cognition can take this long to recover. Following an episode of severe hypoglycemia, patients should not drive for 24 hours. An individual who experiences a severe hypoglycemic episode *whilst driving,* irrespective of whether a crash occurred or not, should be advised to stop driving. A minimum period of a month is recommended, during which time remedial action needs to be undertaken. Specialist review will almost certainly be required. Hypoglycemia in sulphonylurea users can be prolonged, and driving should be stopped for at least 48 hours. Individuals having major changes in therapy (particularly starting insulin treatment) can be temporarily unfit to drive, and may need to stop driving for a few days until it is clear that hypoglycemia is not a difficulty. Individuals who have had their pupils dilated for the purpose of retinal examination are also advised not to drive for two hours. FACTORS FOR MEDICAL PRACTITIONERS TO CONSIDER The aim of determining fitness to drive is to minimize the risk to the individual, and other road users, while maintaining appropriate independence and employment. Medical practitioners should consider the following factors, in addition to the guidance outlined in this chapter, when assessing an individual for fitness to drive: • Type of license held and type of driving undertaken – professional drivers spend up to an entire working week in their vehicle, and that vehicle can weigh greater than 25,000kg or carry many passengers. A crash involving such a vehicle could put many people at risk. Some forms of commercial driving could exacerbate risks of hypoglycemic attacks more than others. • Timing, shifts and total driving hours – hypoglycemia on sulphonylurea drugs and insulin is most common before meals, especially prelaunch, and is also common overnight. Shift work is more of a risk than regular hours, and total driving hours should not be excessive. • Medication – consider the effects of medications, and likely compliance with medications, on the individual's ability to drive safely. • Presence of any complications of the disease – particularly any possible visual impairments. • Individual's motor vehicle crash history (if known) – medical practitioners may need to recommend a longer period of refraining from driving if an individual has a history or pattern of crashes that may be associated with their condition. Where a medical practitioner is aware of a medically related crash, they must inform the Agency if the individual's medical condition remains unresolved and the individual is likely to continue to drive (refer to section 1.4).

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Presence of multiple medical conditions – where an individual has multiple medical conditions, consider any possible combined effects on their ability to drive safely
Alcohol abuse – a possible alcohol-abuse problem may increase the likelihood of hypoglycemic attacks.

DEALING WITH INDIVIDUALS UNFIT TO DRIVE
Medical practitioners can usually successfully negotiate short-term cessation of driving. A person deemed unfit to drive because of severe or recurrent hypoglycemia or with hypoglycemia unawareness should be informed of this by their medical practitioner. Written notification should also be given. The individual should be told how soon they might expect to have this situation reviewed. If a practitioner suspects that the individual is continuing to drive against medical advice, they are legally obliged to inform the Agency under section 18 of the Land Transport Act 1998 (see section 1.4 of this booklet).
4.1 Type 1 diabetes
Individuals in this group are most likely to suffer hypoglycemia, and are also those whose diabetes is most difficult to control. Individuals with unstable diabetes should be reviewed thoroughly before being given permission to drive, and adequate education should be given. Practitioners should be aware of the particular dangers of hypoglycemia in the period after starting insulin therapy, or following major treatment readjustments. Individuals may be temporarily unfit to drive at such times.
4.2 Type 2 diabetes controlled by diet alone
The risks of hypoglycemia may effectively be discounted in this group, and these individuals may be considered fit for all types of driver license. However, a change in the requirements for effective glycemic control (e.g. the introduction of sulphonylurea drugs or insulin) may necessitate the imposition of restrictions. Late complications of diabetes do occur in such individuals.
4.3 Type 2 diabetes controlled by oral hypoglycemic agents
The risk of hypoglycemia is relatively low, but it can occur with the sulphonylurea drugs (tolbutamide, gliclazide, glipizide, glibenclamide) and with meglitinide drugs. It is important that food is not omitted when these tablets are being taken. Individuals should be aware of the risks of hypoglycemia and the danger of drinking alcohol. Metformin when taken without insulin or sulphonylurea drugs does not cause hypoglycemia. The same applies to drugs of the thiazolidenedione group and acarbose. It is important that these individuals are regularly monitored for the emergence of diabetic complications that can affect fitness to drive.
</td></tr>
<tr><td>License classification</td><td>
<table>
<tr><th>License Class</th><th>Motor Vehicles Covered by the License Class</th><th>Normal Requirement for Medical xaminations</th></tr>
<tr><td>Class 1</td><td>

A vehicle that has a GLW or GCW of 4500kg or less (this includes tractors or combinations of vehicles, but does not include motorcycles)
A moped or all-terrain vehicle
Any campervan or tradeperson’s vehicle with a GLW of 6000kg or less and an on-road weight not exceeding 4500kgA tractor with a GLW of more than 4500kg but less than 18,001kg if driven at a speed not exceeding 30km/h
A tractor/trailer combination of more than 4500kg but not more than 25,000kg if being used in agricultural or land management operations and driven at a speed not exceeding 30km/h

</td><td>None</td></tr>
<tr><td>Class 2</td><td>

Any rigid vehicle with a GLW of more than 4500kg but less than 18,001kg
Any combination vehicle (that is not a tractor/trailer combination) with a GCW of 12,000kg or less
Any combination vehicle consisting of a rigid vehicle (that is not a tractor) with a GLW of 18,000kg or less towing a light trailer (GLW of 3500kg or less)
Any rigid vehicle with a GLW of more than 18,000kg that has no more than two axles
A tractor with a GLW of more than 4500kg but less than 18,001kg if driven at a speed exceeding 30km/h
Any vehicle covered in class 1

</td><td>10-yearly</td></tr>
</table>
</td></tr>
</table>

	Class 3	• A combination vehicle with a GCW of more than 12,000kg but less than 25,001kg • Vehicles covered in classes 1 and 2	10-yearly
	Class 4	• A rigid vehicle (including any tractor) with a GLW of more than 18,000kg • A combination vehicle consisting of a rigid vehicle with a GLW of more than 18,000kg towing a light trailer (GLW of 3500kg or less) • Vehicles covered in classes 1 and 2, but not class 3	10-yearly
	Class 5	• A combination vehicle with a GCW of more than 25,000kg • Vehicles covered in classes 1, 2, 3 and 4	10-yearly
	Class 6	• Any motorcycle, moped or all-terrain vehicle	None

Differences in examination requirements between private and commercial drivers

Commercial drivers are expected to meet higher safety standards than other motorists. The Land Transport (Driver Licensing) Rule 1999 defines classes of driver license and types of license endorsement (see appendix 3). This Rule also provides the requirements for obtaining and renewing licenses for the various categories of commercial driver, including the requirement to produce a medical certificate applicable to the class of license or type of endorsement.

Given the potential severity of a crash involving a commercial vehicle, the following commercial type drivers applying for or renewing their license or endorsement must be examined thoroughly:

- Classes 2, 3, 4 or 5
- Passenger endorsement (P)
- Vehicle recovery endorsement (V)
- Driving instructor endorsement (I)
- Testing officer endorsement (O)

The medical examination requirements for lower (private) license classes or endorsement types are generally less than for commercial drivers. Lower license classes or endorsement types include:

- Classes 1 or 6
- The following endorsement types:
  - Dangerous goods endorsement (D)
  - Forklift endorsement (F)
  - Roller endorsement (R)
  - Tracks endorsement (T)
  - Wheels endorsement (W)

Country	Sweden *(1998)*
Source	http://www.vv.se/PageFiles/12660/9889eng000915%5b1%5d.pdf?epslanguage=sv
STANDARD	Chapter 6 Diabetes Mellitus *Possession* 1. Diabetes mellitus that is not under acceptable control with respect to the risk for hypoglycemia constitutes grounds for denial of possession. In the assessment, the risk of unforewarned unconsciousness should be taken into special consideration. On the question of other complications pertaining to diabetes mellitus, the assessment on the danger to traffic safety shall be made in the light of that which is provided elsewhere in these provisions, particularly with respect to traffic vision and cardiovascular diseases. 2. Diabetes mellitus requiring insulin treatment constitutes grounds for denial of possession in Groups II and III. However, if the disease is well balanced, possession in category C may be granted. In such cases, possession shall be limited such that a heavy lorry may not be driven in traffic that is classified as commercial in the provisions of the

<table>
<tr><td></td><td>Commercial Traffic Act (1998:490).
Reappraisal
3. In the case of diabetes mellitus treated with insulin, a reappraisal shall be made after one year and thereafter at least every third year.
General Advice
The three-year interval should be applied only if it can be documented that the disease has been well balanced over a long period of time or has recently been acquired and that shorter intervals are obviously not required.
4. In the case of diabetes mellitus not requiring insulin treatment, a reappraisal shall occur at intervals considered suitable in each individual case. A reappraisal may be omitted if it is obviously unnecessary.
Exception
5. Despite the provisions in Section 2, a person holding a driving license in Group II who acquires diabetes mellitus requiring insulin treatment, may be granted continued possession under the following special circumstances:
a) The disease is will balanced and otherwise without any complications.
b) The holder of the driving license is dependent on the category of license to be able to support himself or has other strongly convincing arguments for retaining possession.</td></tr>
<tr><td>Additional guidance</td><td>Chapter 15 Physician’s Examination

12. When assessing whether a person’s ability to drive a power-driven vehicle is substantially impaired due to diabetes mellitus, particular attention shall be paid to the risk of hypoglycemia. The physician shall be convinced that the applicant, where applicable, is very familiar with the symptoms of hypoglycemia and is aware of the suitable measures to take if such symptoms should arise.
13. Particular attention shall be paid to complications in the vascular system such as retinopathy or neuropathy with symptoms of motor or sensory failure. This also applies to macro-vascular complications with risks of heart or blood vessel diseases.
14. The provisions in Section 12 are particularly applicable to diabetes mellitus that is treated with insulin where the issue concerns qualification to drive a heavy lorry. In such cases, the physician shall assess the applicant’s suitability from a traffic safety point of view to drive such vehicles with respect to the driving and work conditions in question. The physician shall present his opinion on this question in the medical certificate issued.
Chapter 18 Medical Certificate
1. A medical certificate shall be attached to the application for a learners permit for Groups II or III according to Ch.3 Section 1 of the Driving Licenses Ordinance (1998:980). The same thing applies according to Ch.3 Section 6 of the Driving Licenses Ordinance (1998:980) regarding an application for an extension, and according to the SNRA provisions (VVFS 1998:88) on taxi driver licenses in connection with an application for a taxi driver license. Provisions on how the physician’s examination shall be carried out are contained in Chapter 15 of this document. In order to guarantee that the examination of the medical suitability of an applicant complies with the requirements on possession, the medical certificate shall, where applicable, be supplemented with additional information above and beyond the provisions in Section 3.
In general, the certificate or its equivalent shall include a medical statement on whether or not the applicant suffers from a disease that implies a danger to traffic safety.
2. The requirement on further details also applies when the declaration of health contains a statement on a medical condition as provided in Section 3, in the case of a reappraisal and when other information gives reason to question possession of a driving license or a taxi driver license.
General Advice
If a medical condition is unspecified or involves several medical areas, the further details in the background information should primarily be supplemented by a physician specialized as a general practitioner. Further to the provisions in Section 1, the medical certificate should, where necessary, specify the additional information required according to Section 3.
<table>
<tr><th>Functions / Medical Condition</th><th>Basis for Assessment</th></tr>
<tr><td>Diabetes that has not been properly treated or with complications involving serious pathological changes in the blood vessels, in the heart, kidneys, eyes or nervous system</td><td>A certificate issued by a specialist in internal medicine</td></tr>
</table>
</td></tr>
</table>

	Diabetes in other cases	A certificate issued by a specialist in internal medicine or by another specialist who is familiar with the patient's history
	Diabetes that has lasted more than five years or initially appeared after the age of 40	A certificate concerning traffic vision issued: • By an ophthalmologist or • By a physician as provided in the foregoing paragraph, if neither the medical history nor the photograph of the fundus of the eye examined by a person with expert knowledge in the field offers any suspicion on defects in the field of vision. • A certificate concerning traffic vision is not required in the case of a reappraisal after one year according to the provision in Chapter 6, Section 3.
License classification	Group I: Driving license category A, A1, B or BE as well as a tractor license Group II: Driving license category C or CE Group III: Driving license category D or DE as well as taxi driver license Possession: Holding a driving license, tractor license or taxi driver license Reappraisal: Reappraisal of possession through the requirement on a medical certificate or other medical statement A: Heavy motorcycle A1: Light motorcycle B: Private car, light lorry and any light trailer, cross-country vehicle or class I power-driven equipment in tow C: Heavy lorry and any light trailer in tow D: BusE: Trailer, irrespective of number and weight	
Country	United Kingdom *(2009)*	
Source	http://www.dft.gov.uk/dvla/medical/ataglance.aspx	
STANDARD	3. Diabetes Mellitus *STANDARDS FOR GROUP 2 ENTITLEMENT VOC – LGV/PCV* Insulin-treated *(Drivers are sent a detailed letter of explanation about their license and driving by DVLA.)* New applicants on insulin or existing drivers are barred in law from driving LGV or PCV vehicles from 1/4/91. Drivers licensed before 1/4/91 on insulin are dealt with individually and licensed subject to satisfactory annual Consultant assessment. Regulation changes in April 2001 allow "exceptional case" drivers to apply for or renew their entitlement to C1/C1E to drive small lorries with or without a trailer subject to meeting all "Qualifying Conditions". (See Appendix below for full details) Temporary Insulin Treatment *(Includes gestational diabetes, post-myocardial infarction and participants in oral/inhaled insulin trials.)* Legal bar to holding a license while insulin-treated. May reapply when insulin treatment is discontinued. Managed by Tablets Drivers will be licensed unless they develop relevant disabilities, e.g., diabetic eye problem affecting visual acuity or visual fields, in which case refusal, revocation or short period license. If an individual becomes insulin-treated, there will be refusal or revocation. Drivers are advised to monitor their blood glucose regularly and at times relevant to driving, particularly if taking medication likely to cause hypoglycemia such as a sulphonylurea.	

	Managed by Exenatide or Gliptins in Combination with a Sulphonylurea Individual assessment Managed by Diet Alone Need not notify DVLA unless develop relevant disabilities. (e.g., Diabetic eye problems affecting visual acuity or visual field or if insulin required.) Diabetic Complications • Frequent Hypoglycemic Episodes Likely to Impair Driving Refusal or revocation. (Refer to insulin treated standards). • Impaired Awareness of Hypoglycemia Refusal or revocation. (Refer to insulin-treated standards). • Eyesight Complications (Affecting Visual Acuity or Fields) (Refer to insulin treated standards and Section: Visual Disorders) • Renal Disorders (Refer to Section: Renal Disorders) • Limb Disability (e.g., peripheral neuropathy) (Refer to Section: Disabled Drivers at Appendix 1)
Appendix	APPENDIX Police, Ambulance and Health Service Vehicle Driver Licensing* The Secretary of State's Honorary Medical Advisory Panel on Diabetes and Driving has recommended that drivers with insulin treated diabetes should not drive emergency vehicles. This takes account of the difficulties for an individual, regardless of whether they may appear to have exemplary glycaemic control, in adhering to the monitoring processes required when responding to an emergency situation. *Caveat: The advice of the Panels on the interpretation of EC and UK legislation, and its appropriate application, is made within the context of driver licensing and the DVLA process. It is for others to decide whether or how those recommendations should be interpreted for their own areas of interest, in knowledge of their specific circumstances. A Guide for Drivers with Insulin Treated Diabetes who wish to apply for C1/C1E Entitlement Drivers may apply for or renew their entitlement to categories C1/C1+E to drive small lorries with or without a trailer. They may also be eligible to renew category C1E, to drive small lorries with a combined weight of 12 tonnes, if they have passed category CE, although this does not apply if they have previously held CE (102). They will not be entitled by law to hold Category D1 (Minibuses) Qualifying Conditions a person must meet: • They must have had no hypoglycemic attacks requiring assistance whilst driving within the previous 12 months. • They will not be able to apply for category C1 or C1E entitlement until their condition has been stable for a period of at least one month. • They must regularly monitor their condition by checking their blood glucose levels at least twice daily and at times relevant to driving. We advise the use of a memory chip meters for such monitoring • They must arrange to be examined every 12 months by a hospital consultant who specializes in diabetes. At the examination the consultant will require sight of their blood glucose records for the last 3 months. • They must have no other condition, which would render them a danger when driving C1 vehicles. • They will be required to sign an undertaking to comply with the directions of doctors(s) treating the diabetes and to report immediately to DVLA any significant change in their condition.

License classification	The medical standards refer to Group 1 and Group 2 license holders. Group 1 includes motor cars and motor cycles. Group 2 includes large lorries (category C) and buses (category D). The medical standards for Group 2 drivers are very much higher than those for Group 1 because of the size and weight of the vehicle. This also reflects the higher risk caused by the length of time the driver may spend at the wheel in the course of his/her occupation. All drivers who obtained entitlement to Group 1, category B (motor car) before 1 January 1997 have additional entitlement to category C1 and D1. C1 is a medium size lorry of weight between 3.5 and 7.5 tonne. D1 is a minibus of between 9 and 16 seats, not for hire or reward. Holders of C1 and D1 entitlement retain the entitlement until their license expires or it is medically revoked. On subsequent renewal the higher medical standards applicable to Group 2 will apply. Under certain circumstances volunteer drivers can drive a minibus of up to 16 seats without having to obtain category D1 entitlement. Individuals should consult DVLA for a detailed fact sheet.
Country	Mexico (2009)
Source	www.sct.gob.mx/transporte-y-medicina-preventiva/autotransporte-federal/
STANDARD	DIABETES STANDARDS *Reglamento de Tránsito en Carreteras Federales:* Article 59: A person or company shall not permit a driver with the following conditions to operate a federal public service vehicle. 2. Chronic conditions I - Diabetes mellitus. Diabetes insipidus. *Medical-Scientific Profile (Perfil Médico Cientifico)* 6. Endocrine system 6.1 The licensee's internal secretion glands must have anatomical and functional integrity sufficient for the safe and efficient performance of the activities that the license allows. 6.2 In cases where a licensee receives treatment with oral medications that affect the blood sugar level, the licensee must strictly follow the procedures established by the Dirección General de Autotransporte Federal. There must be no evidence of the conditions in 6.3 and 6.4. 6.3 Change in functional ability caused by the internal secretion glands that is incompatible with the safe and efficient performance of the activities that the license allows. 6.4 Diabetes mellitus that the licensee must control with insulin.
Additional guidance	Mexico Physical and Medical Qualification Standards: General Health Regulations *Reglamento de Tránsito de Carreteras Federales* Article 58: Commercial and private transporters must ensure that their drivers hold federal drivers licenses and have adequate experience, capacity, skill, and physical-mental conditions. Article 79: A motor vehicle driver must be in full command of his or her physical and mental abilities, and carry a valid license or a document that replaces it and covers the operation of the vehicle and service that the driver will perform. *Reglamento del Servicio de Medicina Preventiva en el Transporte* Article 9: The licensee must undergo the Integral Psychophysical Exam with the frequency and terms determined in the corresponding Medical-Scientific Profile (Perfil Médico Cientifico), to evaluate his or her state of health and determine if the person is clinically able to conduct driver activities. Article 10: The Integral Psychophysical Exam includes the following. I. Clinical History VI. Cardiology Exam II. General Medical Exam VII. Neurology Exam III. Ophthalmology Exam VIII. Psychology Exam IV. Audiology Exam IX. Laboratory and Clinical Exams

	V. Pulmonology Exam X. Toxicology Exam The Dirreción General de Autotransporte Federal can administer additional exams when it considers it necessary to provide additional evidence that supports a medical judgment or determination. Article 11: The Integral Psychophysical Exam must be conducted in the following situations. I. To solicit or revalidate the Federal Drivers License for each mode of federal transport and its auxiliary services. II. At the detection of any psychophysical change. III. After the occurrence of a transportation accident in which the licensee is involved. IV. When the licensee, shipper, or transporter requests reevaluation. Article 12: The Dirreción General de Autotransporte Federal will give a judgment of Psychophysical Non-Aptitude to drivers who do not fulfill the required conditions laid out in the corresponding Medical-Scientific Profile (Perfil Médico Cientifico). Article 15: The Medical Exam will include the following. I. General inspection II. Meaningful interrogation III. Blood pressure evaluation IV. Balance test V. Ocular and bone/tendon reflex evaluations VI. Exploration of the cardiac area VII. Alcohol usage evaluation The Dirreción General de Autotransporte Federal can administer additional exams when it considers it necessary to provide additional evidence that supports a medical judgment or determination.
License classification	Mexico-domiciled federal-licensed vehicle drivers

Appendix G: Brief History of CMV Driver and Diabetes Policy

Beginning January 1, 1940, the Interstate Commerce Commission's Motor Carrier Safety Regulations (4 FR 2294) began requiring CMV operators to undergo urine glucose testing as part of medical examinations to evaluate whether they were qualified to engage in driving for the purposes of interstate or foreign commerce.(48) The current standard for diabetes was established on January 1, 1971 (35 FR 6458) in response to several risk assessment studies suggesting that diabetic drivers had a higher rate of accident involvement than the general population. On March 28, 1977, comments on proposed changes to this standard were solicited via the Advance Notice of Proposed Rulemaking (ANPRM 42 FR 16452). The prohibition was maintained after a consideration of the comments and the current literature, citing concerns over highway safety (Nov. 1977).(49)

On November 25, 1986, a new ANPRM (52 FR 45204) was issued requesting comments on petitions from two individuals and the American Diabetic Association to eliminate blanket prohibitions on insulin-using CMV drivers, with waivers to be granted to qualified drivers with insulin-treated diabetes on a case-by-case basis. The Conference on Diabetic Disorders and Commercial Drivers (September 1987) was convened to review the diabetes standard in light of new developments in the treatment of diabetics. Conference participants (physicians, scientists, federal officers, and representatives from the motor carrier industry) recommended that waivers could be granted to some drivers depending on conditions such as insulin use, absence of recurrent hypoglycemia, and a safe driving record (Federal Highway Administration, Conference on Diabetic Disorders and Commercial Drivers; Final Report, 1988).(50) In 1990, an ANPRM (55 FR 41208) soliciting comments on a proposal to revise the diabetes standard to allow insulin-treated individuals to operate CMVs if they met certain criteria, and Mellen University and the University of Pittsburgh estimating the various levels of accidents among diabetic drivers depending on the severity of hypoglycemia, was sponsored in conjunction with the ANPRM. The study estimated that an additional 42 crashes would occur each year if the insulin ban was lifted.(51) This increase was considered acceptable and a Notice of Intent to Issue Waivers was released in 1992.

A diabetes waiver program was established in 1993 as part of a research study to investigate whether drivers with insulin-treated diabetes admitted to the program could safely operate CMVs. Participating drivers were required to have a minimum of three years of recent CMV driving experience while using insulin, a safe driving record, and certification by an endocrinologist and an ophthalmologist. The waiver program was set to last for three years, or until resolution of the concurrent rulemaking action, whichever occurred first.

In 1996 the District of Columbia Court of Appeals ruled in *Advocates for Highway and Auto Safety versus Federal Highway Administration* that a vision waiver program was contrary to law in that it "was devoid of empirical support in the record" (meaning that the initial determination that the vision waiver program would not adversely affect the safe operation of CMV was not defensible through data). Since the diabetes waiver program used an approach to pre-qualification of drivers that was similar to that of the vision waiver program, it too was terminated. Drivers then holding a diabetes-related waiver were allowed, under "grandfather" provisions (49 CFR 391.64), to continue to operate CMVs in interstate commerce.

The Transportation Equity Act for the 21st Century (June 9, 1998, TEA-21; Pub. L. 105-178, 112 Stat. 107) directed an inquiry into the feasibility of developing a safe and practical program for allowing individuals with insulin-treated diabetes to operate CMVs interstate.(52) This inquiry was required to evaluate research and other relevant information on the effects of insulin on driving performance, consult with individual state programs for CMV operation by drivers with insulin-treated diabetes, evaluate the Department of Transportation's (DOT) policies in other modes of transportation, analyze pertinent risk data, consult with interested groups knowledgeable about diabetes and related issues, and assess the possible legal ramifications of permitting individuals with insulin-treated diabetes to operate CMVs in interstate commerce. The findings of this inquiry were to be reported to Congress, along with the elements of a protocol to permit individuals with IDDM to operate CMVs (should such a program prove feasible). In addition, TEA-21 provided for the administration of waivers and exemptions for persons seeking regulatory relief from statutes governing insulin-treated diabetes and CMV interstate operation. Depending on the nature of the request, these waivers and two-year exemptions (49 U.S.C. 31315 and 31136[e]) were required to go through a period of public comment via release in the *Federal Register*.

The results of the report authorized under TEA-21 were submitted to Congress on August 23, 2000, with the conclusion that a safe and practicable protocol to allow some IDDM individuals to operate CMVs was feasible. The report included a then-current review of the literature on the risk of driving with diabetes.(53) As the literature review detailed, there was no consistent trend in the risk of automobile crashes related to diabetes, although many studies suffered from flawed methodology, and none directly addressed CMV operation.

The Federal Motor Carrier Safety Administration (FMCSA) published a notice of intent to issue exemptions from the regulations of 49 CFR 391.41[b][3](54) to qualified insulin-dependent diabetes mellitus CMV drivers in the *Federal Register.* The duration of the exemption was limited to two years and could be renewed. The exemption could be immediately revoked if: the person failed to comply with the terms and conditions of the exemption; the exemption resulted in a lower level of safety than was maintained before the exemption was granted; or if continuation of the exemption was inconsistent with the goals and objectives of the regulations issued under the authority of 49 U.S.C. 31315 and 31136[e]. FMCSA did not amend its diabetes standard.

The 2003 FMCSA diabetes exemption process had three components. The first was a screening component to identify qualified applicants. This process examined the applicant's experience and safety in operating CMVs with insulin-treated diabetes, history of hypoglycemia, and the results of examinations by medical specialists. One important requirement in the screening process was that applicants should have three years of safe CMV driving experience while using insulin. The second component provided guidelines for managing diabetes while operating a CMV, including supplies to be used and the protocol for monitoring and maintaining appropriate blood glucose levels. The last component specified FMCSA's process for monitoring insulin-treated commercial drivers. The specifications addressed the required medical examinations and the schedule for their submission. In addition, these specifications indicated how glucose measures should be taken and reviewed, and how episodes of severe hypoglycemia and accidents should be reported.

Since that exemption program began in 2003, FMCSA received 154 applications, and had granted exemptions in five cases. The remaining 149 cases were pending as of November 2005. Exemption

denials have clustered into three groups, according to FMCSA: applicants with limited driving experience, insufficient length of time documenting the medical condition, and poor driving records.(55)

On February 12, 2004 the Senate Highway Funding Bill – Truck Safety Provisions Sec. 4229 (Anti-Safety Provision) – announced the following decisions in the section entitled *Operation of Commercial Motor Vehicles by Individuals who Use Insulin to Treat Diabetes Mellitus*:

- Directed the Secretary to issue a rule to provide for individual assessments of commercial driver's license (CDL) applicants who use insulin to treat diabetes;
- Statutorily exempted diabetic drivers from current medical requirements and from need to make application to FMCSA diabetes exemption program;
- Stated the rule may require CDL applicants with diabetes to have used insulin for a minimum period of time and to demonstrate stable control of their diabetes;
- Eliminated the requirement that CDL applicants with diabetes have previous experience driving a CMV.(56)

Safe, Accountable, Flexible and Efficient Transportation Equity Act: A Legacy for Users (SAFETEA-LU), of August 2005 required FMCSA to revise the terms and conditions used to issue exemptions to certain insulin-treated diabetic drivers of CMVs from the diabetes mellitus prohibitions contained in the FMCSRs. Drivers with insulin-treated diabetes mellitus (ITDM) who met the modified criteria were able to request an exemption from 49 CFR 391.41(b)(3).(57)

The issue of diabetes mellitus and CMV operator qualifications was revisited in the November 8, 2005 *Federal Register* (Vol. 70, Number 125), which announced a revision of the terms and conditions of its previous decision to issue exemptions to certain CMV drivers with insulin-treated diabetes. These revisions were in response to section 4129 of SAFETEA-LU, which required FMCSA to modify its exemption program to allow individuals who use insulin to treat diabetes mellitus to operate CMVs in interstate commerce without having to demonstrate safe driving experience operating a CMV while using insulin, while at the same time implementing certain other requirements in section 4129.(58)

As required by section 4129(b)(c), these changes are: (1) elimination of the requirement for three years of experience operating CMVs while being treated with insulin; and (2) establishment of a specified minimum period of insulin use to demonstrate stable control of diabetes before being allowed to operate a CMV. In addition, Section 4129(d) directed FMCSA to ensure that drivers with insulin-treated diabetes would not be held to a higher standard than other drivers, with the exception of limited operating, monitoring, and medical requirements deemed medically necessary.

On March 17, 2006, FMCSA published an Advance Notice of Proposed Rulemaking (ANPRM docket number FMCSA 2005-23151) to begin a re-evaluation of the rule that prohibits drivers with insulin-treated diabetes from operating CMVs. Public comments and the advice of the newly appointed Medical Review Board were considered in the evaluation of potential changes to the existing medical standards. The deadline for comment submission was June 15, 2006.(48)

Appendix F: Treatment by Individual States of CMV Drivers with IDDM

Reflecting the option to apply the FMCSRs to medical qualifications of intrastate operators of CMVs, individual states vary widely in how they deal with CMV drivers with insulin-treated diabetes. As demonstrated in the table above, states vary in whether they allow drivers with insulin-treated diabetes to operate CMVs. Other states have "grandfathered" drivers who were operating a CMV, while disallowing new drivers with insulin-treated diabetes to obtain a CDL. Below is a brief summary of each state's treatment of intrastate CMV drivers with IDDM.

Alabama

The state of Alabama follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41. CMV drivers with insulin-treated diabetes who practiced before the ruling are "grandfathered."

Alaska

The state of Alaska requires all CMV drivers to carry a medical card (certificate of medical examination) at all times when operating a commercial vehicle.

Arizona

In the state of Arizona, CDL drivers are required by law to keep a current DOT medical examination report and medical examiner certificate on file with the state's Motor Vehicle Division. Exemptions for diabetes are available through the FMCSA.

California

In the past, California issued restricted licenses to intrastate CMV drivers with insulin-treated diabetes who did not meet FMCSA standards, but in general, the licensing of these individuals is rare. The restricted license may include a scope of employment restriction specific to the individual's current job, restrictions against transporting hazardous materials or operation of vehicles requiring a passenger endorsement. Drivers with insulin-treated diabetes who receive a restricted license are generally diabetics who initially controlled the disease with oral drugs and have progressed to insulin use.

Colorado

Drivers not physically qualified to drive a commercial motor vehicle as required by 49 CFR 391.41, may apply for a Colorado State Patrol intrastate medical waiver. The authority to issue medical waivers was adopted by Colorado under the authority of 42-4-235, CRS. Waivers are issued to individuals who have failed to meet the requirements of 49 CFR 391.41 for the following conditions:

- 391.41(b)(1)and(b)(2)-Loss of limb
- 391.41(b)(3)-Clinical diagnosis of diabetes mellitus currently requiring insulin for control
- 391.41(b)(10)-Vision requirements

Connecticut

A person has the option of applying for a Connecticut Department of Motor Vehicle CDL intrastate medical exemption regarding the following medical conditions or impairments:

- Vision impairment in one eye
- Insulin-dependent diabetes
- Loss of or loss of use of limb

District of Columbia

The District of Columbia follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Delaware

If an individual does not meet 49 CFR Part 391.41 Physical Qualifications for Drivers, they may be able to obtain a Delaware intrastate-only restricted CDL medical waiver, if otherwise qualified to drive a motor vehicle (excluding transporting passengers or hazardous materials).

Florida

The state of Florida follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Georgia

The state of Georgia follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Hawaii

As a result of Act 18, 2003 Session Laws of Hawaii, certain insulin-using diabetic drivers who do not meet the federal minimum health standards for a commercial driver's license, will now be able to apply for a restricted (intrastate-only) CDL. These drivers will need to meet the requirements for an intrastate medical waiver adopted by the director of transportation.

Idaho

The state of Idaho follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Illinois

Illinois currently allows CMV drivers with insulin-treated diabetes who have been eligible, licensed, and operating a CMV prior to July 29, 1986 to operate CMVs with a gross vehicle weight rating (GVWR) or gross combination weight rating (GCWR) of 12,001 lbs. or more. Illinois also allows CMV drivers with insulin-treated diabetes to operate under restriction.

Indiana

The state of Indiana follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Iowa

The state of Iowa follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Kansas

Kansas follows the FMCSRs for drivers transporting passengers in a vehicle that is not owned by a city or county. These drivers must also carry a medical card that certifies their fitness to drive. Kansas Statute 66-1,129 (c) excludes motor vehicles owned and operated by "any municipality or any other political subdivisions of this state." In addition, in Kansas there is no process for a diabetes waiver for CDL drivers with a passenger endorsement

Kentucky

Kentucky issues medical waivers for CMV drivers with insulin-treated diabetes not meeting certain FMCSA standards. Waiver applications include a completed medical examination form and supplemental medical form. Other factors considered in the waiver application include driving record, uncontrolled diabetes, and a history of diabetic shock or coma.

Louisiana

The state of Louisiana Office of Motor Vehicles places a restriction ("K") on CDLs of drivers with a medical and/or visual problem that disqualifies them from driving outside the state of Louisiana.

Maine

The state of Maine follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41, unless they will be driving school buses.

Maryland

In the state of Maryland, individuals who have diabetes and do not meet 49 CFR Part 391.41(b)(3) may submit a request for consideration of an intrastate waiver. Extensive documentation such as a health questionnaire, endocrinologist evaluation, and diabetic education verification will be required as well as a review by the Driver Wellness & Safety Division.

Massachusetts

The Registry of Motor Vehicles may issue an intrastate waiver for a diabetic condition if: the individual submits a written statement from his or her physician which: provides specific reasons why the individual is not at risk or is no longer at risk of suffering hypoglycemic spells or episodes; and recommends a specific date for the registry to re-evaluate the individual's ability to operate a commercial motor vehicle safely.

Michigan

Unless considered exempt by FMCSA, CMV drivers must comply with all federal commercial driver qualification requirements. This includes drivers who operate commercial vehicles only in Michigan.

Minnesota

In the state of Minnesota, under certain circumstances, an intrastate driver may be granted a waiver from the following physical qualification requirements: vision, insulin-dependent diabetes, deaf and hard of hearing, and limb impairment.

Mississippi

The state of Mississippi issues intrastate CDLs to diabetic drivers (who are otherwise eligible for CDLs) that demonstrate that they are free from insulin reactions and are able to manage their diabetes effectively.

Missouri

The state of Missouri follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41

Montana

The state of Montana follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Nebraska

The state of Nebraska follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Nevada

The state of Nevada issues medical waivers to intrastate CMV drivers with IDDM. Eligible applicants must be free from having suffered any fainting or dizzy spells, seizures or other similar disorders in the preceding one year.

New Hampshire

A person who cannot meet the FMCSA medical requirements may apply to the Commissioner of Safety for a New Hampshire intrastate waiver.

New Jersey

The state of New Jersey follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41

New Mexico

The state of New Mexico follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

New York

New York allows CMV drivers with insulin-treated diabetes to operate buses with proof that the operator has been free of incidents of hyperglycemia or hypoglycemia shock in the past two years. The operator must be under medical supervision, with written certification provided by the physician biannually. CMV drivers with insulin-treated diabetes who do not drive buses are not regulated unless they suffer a loss of consciousness; those who suffer such an incident are subject to regulations and may have to be incident-free to continue driving prior to agency approval.

North Carolina

The state of North Carolina issues intrastate-only CDLs to applicants who can furnish the following: a completed DOT physical report, statement from treating physician(s) with brief explanation of disability, letter from employer stating driving needs.

North Dakota

The state of North Dakota follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Ohio

The state of Ohio issues intrastate-only CDLs to drivers who are unable to pass the regular "USDOT physical exam" found in 49 CFR Part 391.41.

Oregon

Oregon has provided limited exemptions and waivers for CMV drivers with insulin-treated diabetes since 1984. The exemptions and waivers are subject to medical requirements.

Rhode Island

The state of Rhode Island follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

South Carolina

The state of South Carolina follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

South Dakota

The state of South Dakota seems to issue medical waivers ONLY to otherwise-eligible school bus drivers with IDDM.

Tennessee

The state of Tennessee issues restricted (intrastate-only) CDLs for applicants with insulin-controlled diabetes.

Texas

Texas does not issue exemptions for CMV drivers with insulin-treated diabetes.

Utah

Utah allows medical waivers to be issued with the following requirements: an extensive medical history check for the past five years, a driving record check, a complete medical examination by an internist or endocrinologist, ongoing monitoring and re-evaluation requiring self-testing and recording of results by the CMV operator. The waiver must be renewed either annually or biannually on the recommendation of the operator's health care professional.

Vermont

Issuance of waivers allowing otherwise-eligible CMV drivers with IDDM to obtain CDLs is at the State Commissioner's discretion only. Applicants are encouraged to submit all documentation that strongly demonstrates their ability to control their diabetes and remain free from adverse IDDM-related reactions.

Virginia

The state of Virginia follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

Washington

In the state of Washington, applicants who do not meet the medical requirements of 49 CFR Part 391.41, but whose condition is stable, and who possess a CDL from another state, can apply for a medical waiver for intrastate driving.

West Virginia

In the state of West Virginia, applicants who cannot meet the FMCSA physical qualifications, may submit the following to determine eligibility for an intrastate medical waiver: a CDL application, DOT medical certificate, a letter from a physician stating the reason for the disqualification and his/her opinion as to whether the condition would interfere with the safe operation of a commercial motor vehicle.

Wisconsin

The state of Wisconsin follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements, unless they are a school bus driver, or employed by a political subdivision.

Wyoming

The state of Wyoming follows the FMCSRs and does not allow IDDM individuals to obtain a state-issued waiver from the requirements of 49 CFR Part 391.41.

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