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Systematic Evidence Review
Number 19

Screening for Type 2 Diabetes Mellitus

Prepared for:
U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality
6010 Executive Boulevard, Suite 300
Rockville, Maryland 20852
http://www.ahrq.gov

Contract No. 290-97-0011
Task Order No. 3
Technical Support for the U.S. Preventive Services Task Force

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February 4, 2003

Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Context: Type 2 diabetes mellitus (DM-2) is an important cause of morbidity and mortality for individuals and the US population. Many people have DM-2 but have not been diagnosed. Whether screening to detect and treat DM-2 would do more good than harm is not clear.

Objective: To examine the evidence of the benefits and harms of screening and earlier treatment in reducing the complications of this disease to assist the US Preventive Services Task Force.

Data Sources: We identified English language articles on the following: yield of screening, the risk of complications, the effectiveness of treatments to reduce complications for those with clinically detected DM-2, the harms of screening and earlier treatment, the effectiveness of treatments aimed at those with impaired fasting glucose or impaired glucose tolerance (IFG/IGT), the effects of treatment on quality of life, and the costs and cost-effectiveness of screening. To identify these articles, we searched the MEDLINE database from 1966 through November 7, 2001; searched the Cochrane database of systematic reviews through 2001; examined reference lists of textbooks, monographs, and review articles; and asked experts in the field.

Study Selection: To determine the yield of screening, we examined studies of the results of population-based screening. We included studies of population screening that compared one test against another, examined the ability of a test to detect pathologic evidence of diabetes, or examined the reliability of screening tests. To determine the risks of complications, we included longitudinal studies of recently diagnosed people with DM-2 of at least 1 year's duration. For the

effects of treatment on numerous intermediate and four health outcomes, we examined randomized controlled trials (RCTs) of treatments for various diabetic complications. To determine the harms, costs, and cost-effectiveness of screening, we examined all study designs concerning these outcomes. We also examined all study designs of population-based groups for the effects of lifestyle interventions or medications in reducing the incidence of DM-2 among those with IFG/IGT.

Data Extraction: We abstracted the following data from included articles that dealt most directly with our key questions: demographic details about study subjects, how study subjects were selected, inclusion and exclusion criteria, drop-out and loss-to-follow-up rates, study design and duration, how randomization was accomplished, interventions and co-interventions, measurement methods, and outcome results. We evaluated the internal validity, external validity, and coherence of results of each individual study and assessed all the evidence concerning each key question.

Data Synthesis: No large RCT of screening has been performed. Thus, the evidence for the benefits of screening is indirect. A detectable preclinical period exists, but its length is uncertain. Screening tests with adequate accuracy, reliability, and acceptability are available. The health outcomes of blindness, chronic renal failure, and lower extremity amputation occur infrequently until 20 years or longer of diabetes duration. Trials of treatment after clinical diagnosis have found it difficult to demonstrate a statistically significant health benefit. How much these outcomes would be reduced by the additional few years of treatment produced by screening is uncertain. Visual impairment less severe than blindness and cardiovascular (CVD) events are more common complications in the decade after diabetes diagnosis. Tight control of blood

pressure is effective in reducing these complications among those already clinically diagnosed with DM-2 and hypertension. Little information is available about harms of screening, although several harms are potentially serious problems. The costs of diagnosis, treatment, and dealing with the complications of DM-2 are high. One study examined the cost-effectiveness of screening for DM-2 but assumed that the only effective treatment was glycemic control.

Conclusion: The evidence for screening for DM-2 is indirect and mixed. The strongest case for screening comes from earlier detection and treatment of CVD risk factors, especially hypertension. An RCT of screening is needed to answer the many remaining questions.

Keywords: diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, visual impairment, retinopathy, blindness, chronic renal failure, lower extremity amputation, cardiovascular disease, hypertension, dyslipidemia, glycemic control, laser photocoagulation

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Chapter 1. Introduction

The burden of suffering caused by type 2 diabetes mellitus (hereafter DM-2) is enormous. Studies in the United States have shown that nearly 10% of people who have had DM-2 for 20 years or longer are legally blind.[1,2] About 25% of diabetics over the age of 18 report some difficulty with vision.[3] About 33% of people undergoing renal replacement treatment (ie, dialysis or transplant) have end-stage renal disease primarily attributable to diabetes,[4] about half of these due to DM-2.[5] About half of all lower extremity amputations in the United States occur in diabetics.[6,7] The risk for cardiovascular disease (CVD), including both coronary heart disease (CHD) and stroke (cerebrovascular accident [CVA]), is 2 to 4 times greater in diabetics than nondiabetics with the same age and CVD risk status.[8-21] Diabetics report 2 to 3 times more activity limitations than nondiabetics.[22]

In addition to these real human costs, in 1997 the US health care system spent some $98 billion on medical care and lost productivity for people with diabetes. Per capita medical costs for diabetics were nearly 4 times those for nondiabetics.[23]

The incidence and prevalence of DM-2 in the United States are increasing.[24-28] Based on national data from the National Health and Nutrition Examination Survey (NHANES III, 1988-1994), the prevalence of diabetes (both diagnosed and undiagnosed) among people ages 40 to 74 years (the great majority of whom have DM-2) increased from 8.9% for the period 1976 to 1980 to 12.3% for the period 1988 to 1994.[25]

National data have demonstrated convincingly that many people who satisfy the criteria for DM-2 have not been diagnosed and are thus not under medical care for this condition. For example, NHANES-III found that 5.3% of the adult population ages 20 and older had been

previously diagnosed with diabetes but that another 2.8% had not been diagnosed and yet met diagnostic criteria.[25,29] Such data, combined with new information from randomized controlled trials (RCTs) of treatment of people with DM-2, have raised the question of whether screening and early treatment would reduce the burden of suffering caused by this condition.

For screening to be effective in decreasing the complications of DM-2, we must first demonstrate the existence of a detectable preclinical period and of acceptable and accurate screening tests to detect the disease during that period. The efficacy of treatments for patients with existing disease is well established.[30-34] Screening is justified only if it offers incremental benefit beyond this level of efficacy (see Figure 1, the "delta question" diagram). Specifically, do treatments started at screening diagnosis reduce the incidence of complications (Line C, Figure 1) below that which would be expected with customary clinical detection (Line B)? The "delta" (i.e., difference between lines B and C) is the reduction in the incidence of complications achieved by starting earlier rather than later. Finally, we must also show that the inevitable harms and financial costs associated with screening and earlier treatment are small enough that they do not outweigh the benefits of earlier treatment.

In its review of this topic in 1996, the US Preventive Services Task Force (USPSTF) concluded there was "insufficient evidence to recommend for or against routine screening for diabetes mellitus in asymptomatic adults."[35] The Task Force cited the lack of a practical, accurate screening test and insufficient evidence that detection of diabetes in the asymptomatic period significantly improves long-term outcomes.

In a 2002 policy statement, the American Diabetes Association indicated that screening every 3 years should be considered for all people beginning at age 45 and for younger people with such risk factors as family history, overweight, minority race or ethnicity, previously

identified impaired fasting glucose or impaired glucose tolerance, hypertension, high density lipoprotein cholesterol 35 mg/dl or less, or history of gestational diabetes or delivery of a baby weighing more than 9 pounds.[36]

Chapter 2. Methods

Analytic Framework and Key Questions

To complete this systematic evidence review (SER) for the US Preventive Services Task Force (USPSTF), we developed an analytic framework (Figure 2) and 6 key questions (Table 1) to quantify the benefits, harms, and costs of screening for type 2 diabetes mellitus (DM-2). The analytic framework describes the relationship between screening a population at risk for asymptomatic diabetes and 4 critical health outcomes: severe visual impairment, chronic renal failure (ie, end-stage renal disease), lower extremity amputations, and macrovascular endpoints (cardiovascular disease [CVD] events). Early treatments and intermediate or health outcomes that they affect include: laser photocoagulation for retinopathy; tight glycemic control for retinopathy, albuminuria, foot ulcers, and macrovascular endpoints; tight blood pressure control for retinopathy, hypertension, and macrovascular endpoints; angiotension-converting enzyme (ACE) inhibitors and angiotension receptor blockers (ARBs) for albuminuria and macrovascular endpoints; foot care programs for foot ulcers; and lipid control for dyslipidemia. In this logic model, tight glycemic control and tight blood pressure control relate to all 4 health outcomes; laser photocoagulation to severe visual impairment, foot care programs to lower extremity amputations, and lipid control to cardiovascular events. Finally, prevention (below the screening arrow) concerns the question of early detection and treatment of impaired fasting glucose or impaired glucose tolerance and, in theory, primary prevention of the complications shown as the 4 major health outcomes. The arrows in the analytic framework thus represent steps in the chain

of logic connecting screening with these 4 outcomes; the numbers in parentheses are key questions in Table 1.

Search Strategy

We identified studies in the English language by searching the MEDLINE database from 1966 through November 7, 2001. Apart from formal searches, we examined reference lists of textbooks, monographs, and review articles, and we queried experts in the field.

All MEDLINE searches included the term "NIDDM" and a wide range of additional terms: risk retinopathy, nephropathy, neuropathy, cardiovascular disease, stroke, visual impairment, chronic renal failure, lower extremity amputation, mass screening, glucose tolerance, costs and cost-effectiveness, harms (psychological, drug related), primary prevention, cataracts, and quality of life. Searches for the key questions on treatment efficacy added terms for the specific treatments; these included, for example, angiotension-converting-enzyme inhibitors, calcium channel blockers, diet, and glycemic control (with either insulin or oral agents), HMG co-A reductase inhibitors, photocoagulation, and physical activity, as well as terms for "randomized controlled trial."

Our search strategy involved 2 phases. The first used broad search terms and review criteria to maximize the probability of identifying all potentially relevant articles. The second applied more stringent criteria to focus on those studies directly applicable to the key questions.

The first author and at least 1 other author or physician consultant independently reviewed the titles and abstracts of the 4,983 articles and selected 1,557 as most relevant to the key questions. Of these, we retained and abstracted data from 44 that met the stringent inclusion

criteria and most directly addressed the key questions. Data describing studies (trials, observational studies, and meta-analyses) and their results were recorded in the evidence tables.

Production of the Systematic Evidence Review

The project team included representatives from the Research Triangle Institute-University of North Carolina at Chapel Hill Evidence-based Practice Center and 3 representatives from the US Preventive Services Task Force. The entire Task Force discussed the SER's work plan, evidence tables, and preliminary text at several meetings and provided overall guidance. A draft SER was subjected to extensive external peer review (see Acknowledgments, Appendix A) and we revised the SER accordingly. A shorter version of the work[37] accompanies the USPSTF Recommendations and Rationale statement on this topic.

Chapter 3. Results

Our presentation of results is arranged chiefly in accordance with the 6 key questions (KQ) introduced in Chapter 2 and Table 1. Specifically, we address the following issues: presence of a detectable preclinical period for DM-2; properties of diabetes screening tests (KQ No. 2); efficacy and effectiveness of various treatments (KQ No. 3); including interventions for persons with IFG or IGT (KQ No. 4); harms of screening or earlier treatment (KQ No. 5); and costs and cost-effectiveness (KQ No. 6). For KQ No. 3 on therapies, we organize the discussion in terms of the four major health outcomes – vision impairment, chronic renal failure, lower extremity ulcers or amputations, and cardiovascular events (myocardial infarction, stroke, cardiovascular death) – specified in the Analytic Framework (Figure 2).

Studies meeting our inclusion criteria that provide data for the sections that follow appear in one or more of the 9 evidence tables found in Appendix B. Those tables contain abstracted information on the following topics:

- Properties of screening studies (KQ 2)(Evidence Table [ET] 1);
- Treatment studies (KQ 3): impact of tight glycemic control (ET 2); studies on antihypertensives and angiotensin interruptors (ET 3); laser photocoagulation for visual impairment (ET 4); foot care and lower extremity amputation (ET 5); lipid-lowering medications for cardiovascular disease (ET 6);
- efficacy of lifestyle interventions for persons identified on screening as having IFT/IGT (KQ 4) (ET 7);
- harms of screening or treatment (KQ 5) (ET 8); and
- costs and cost-effectiveness (KQ 6) (ET 9).

Presence of a Detectable Preclinical Period

Many people not known to have DM-2 meet criteria for this disease.[25] Thus, the natural history of DM-2 often includes a detectable preclinical period, but the length of this period is uncertain. One can estimate the length of this period by (a) extrapolating backward in time from the prevalence of retinopathy at various times after clinical diagnosis to the presumed time when retinopathy begins[38] and (b) then adding to that an estimate of the time after disease origin when retinopathy becomes apparent.[39] Using these two estimates, some have suggested that the detectable preclinical period has a mean length of 10 to 12 years and that systematic screening would detect the disease at an average of 5 to 6 years before clinical diagnosis.

The length is important because any added benefit of screening must be produced by effective treatment during this preclinical period. If the period is short, then the treatment will have limited time to influence outcomes. Only a randomized controlled trial (RCT) of screening can accurately determine the length of the detectable preclinical period.

The classification of diabetes includes an intermediate category, "impaired glucose tolerance" (IGT, used when the glucose tolerance test defines the disease) or "impaired fasting glucose" (IFG, used when the fasting plasma glucose defines the disease). Criteria for these conditions include a 2-hour post-load plasma glucose (or a fasting plasma glucose) above the "normal" range but below the "diabetic" range. People in this intermediate category would also be detected by screening. Although not everyone with IFG/IGT progresses to DM-2, the group as a whole manifests an increased risk of developing DM-2. Thus, the preclinical period for DM-2 includes both a "pre-detection" period (during which people meet diagnostic criteria but have not been diagnosed) and an earlier "pre-disease" period (during which people do not yet meet diagnostic criteria but are at increased risk).

Accuracy and Acceptability of Screening Tests

Key Question No. 2 dealt with the yield of screening, including accuracy and reliability of the various tests. Determining the accuracy of screening tests for DM-2 is complicated by the uncertainty about the most appropriate "gold standard" for comparison. Ideally, the gold standard should be the test that best distinguishes persons who do not develop complications from those who do. Data on studies relevant to these issues are presented in Evidence Table 1 (Appendix B). Our main finding, discussed here, is that although no test is perfect, several screening tests with adequate acceptability and accuracy for DM-2 are available.

Three large population-based studies have examined the sensitivity of 3 potential screening tests in detecting existing retinopathy among those not previously diagnosed as diabetic. The tests are the 2-hour post-load plasma glucose (2 hr PG), the fasting plasma glucose (FPG), and the hemoglobin A1c (Hb A1c). At current nationally used cutpoints (FPG ≥ 126 mg/dl; 2 hr PG ≥ 200 mg/dl; Hb A1c > 6.4%), both sensitivity and specificity for detecting retinopathy were in the range of 74% to 88% for all 3 tests.[40-42] One of these studies also examined the performance of the 3 tests in predicting future retinopathy, finding that they each performed about the same.[40]

Other studies have examined whether these 3 tests predict future cardiovascular disease (CVD). In a recent meta-regression analysis of 20 observational studies, Coutinho et al found that both FPG and 2 hr PG were significantly associated with future CVD events.[43] The association was curvilinear with the greatest risk at the highest glucose levels, but some increased risk persisted below the current cutpoint for DM-2 (i.e., FPG ≧ 126 mg/dl; 2 hr PG ≥ 200 mg/dl). The Coutinho et al analysis was not able to determine to what extent this association was independent of other CVD risk factors, but later work has shown that only part of the

increased risk is explained by other known risk factors.[44,45] These findings are seen also in other, more recent studies, which include Hb A1c as well as FPG and 2 hr PG.[44,46,47]

Although all these tests can detect or predict diabetes complications, their results are not identical. Because diabetics often develop postprandial hyperglycomia before fasting hyperglycemia, the 2 hr PG test is more often abnormal than the FPG.[29] Using a 2 hr PG of ≥ 200 mg/dl as the reference standard, Harris et al showed that the specificity of an FPG ≥ 126 mg/dl is greater than 90% and that the sensitivity is about 50%.[29] According to Blunt et al, the sensitivity may be lower for people older than age 65 years.[48]

Among the general, previously nondiabetic population of people ages 40 to 74 years in NHANES III (prevalence of 2 hr PG ≥ 200 mg/dl of 6.6%), a person with an FPG of 140 mg/dl or greater has a 91% probability of having a 2 hr PG of ≥ 200 mg/dl. For an FPG of 110 to 126 mg/dl, the probability is 18%.[29]

Hb A1c is not sensitive to lower-level elevations of FPG. Among persons meeting the current definition of IFG (110 to 125 mg/dl) in one large study, Hb A1c was normal (less than or equal to 6.1%) in nearly 87% of those tested.[49] Among those with previously undiagnosed DM-2 who are in the low range of "diabetic level" FPG (ie, FPG between 126 and 140 mg/dl), Hb A1c was normal in about 60% of those tested.

Some experts have argued that excessive glycosylation, as exemplified by Hb A1c, is an important intermediate step in some of the microvascular complications of DM-2. By this reasoning, persons with lower levels of hyperglycemia should also have an elevated Hb A1c before any conclusive diagnosis is made.[49]

A single 2 hr PG is less reproducible than an FPG.[50] The Hb A1c assay has not been completely standardized, although the National Glycohemoglobin Standardization Program has

made progress in this direction.[51] Because of individual differences in glycosylation and red blood cell turnover, Hb A1c varies more between individuals than within nondiabetic individuals, thus raising questions as to whether any screening cutpoint can be determined for a large group of people.[52]

In clinical practice, the requirement for a screening test to be either fasting (as with the FPG) or post glucose load (as with the 2 hr PG) presents logistical problems. A well-conducted, population-based study found that random capillary blood glucose (CBG) had sensitivity and specificity in the 75% to 80% range for detecting DM-2 defined by older criteria (i.e., FPG ≥ 140 mg/dl or 2 hr PG ≥ 200 mg/dl) if results were interpreted according to age and time since last meal.[53] Another analysis found a sensitivity of 75% to 84% and a specificity of 88% to 90% in primary care populations for a random CBG with a cutpoint of 126 mg/dl.[54]

Efficacy and Effectiveness of Treatment

We review here whether treatments affect any of the 4 health outcomes shown in Figure 2: namely, visual impairment, chronic renal failure, lower extremity amputations, and CVD events. The analysis also tries to clarify the "delta" question reflected in Figure 2, that is, whether early treatment started at screening diagnosis will yield benefits (reduce complications over and above those produced from treatments started at clinical diagnosis.

Evidence Tables 2-6 (Appendix B) deal with the main therapeutic approaches that are used singly or in combination to address these clinical issues. We also examine the evidence that treatments aimed at those people with IFG or IGT (IFG/IGT), a group frequently identified through screening, produce a difference in these diabetic complications.

The most compelling evidence for a difference in the incidence of health outcomes between those diabetics detected by screening and those identified by clinical detection would come from an RCT of screening. Several recent RCTs of treatment (comparing Lines A and B in Figure 1) have been conducted. However, no RCT of screening for DM-2 (comparing Lines B and C) has yet been done; as noted earlier, this means no direct evidence answers KQ No. 6. Thus, the evidence we review in this section is necessarily indirect, requiring extrapolation to answer our remaining key questions.

Screening for DM-2 involves a further complexity. The alternative to screening is not the absence of screening because the latter already occurs "haphazardly" through incidental blood work and urine screening. Surveys in the United States have found that about 30% to 40% of people more than 45 years of age report having been screened for DM-2 within the previous year.[55,56]

Our interest in this review, however, is to compare the health outcomes between a strategy of no screening and a strategy of systematic (not haphazard) screening. In this review, we use the term "clinical detection" for Line B (meaning detection by clinical symptoms or associated conditions) and the term "screening detection" for Line C (meaning detection by systematic screening); we do not consider the consequences of haphazard screening.

Severe Visual Impairment

Diabetes affects vision in at least 3 ways. First, diabetics develop changes in retinal blood vessels – diabetic retinopathy (including its related condition, macular edema) – not generally seen in nondiabetics. In addition, diabetics develop cataracts and glaucoma more

frequently than nondiabetics. Most diabetes-related visual impairment is associated with retinopathy, and thus our review will focus on this area.

Incidence and Prevalence of Retinopathy and Visual Impairment

The prevalence of any retinopathy increases from about 8% to 10% at screening diagnosis to about 21% at clinical diagnosis.[57-59]

The prevalence of the most severe form of retinopathy ("proliferative diabetic retinopathy") is less than 1% at both screening and clinical diagnosis. The prevalence of retinopathy of intermediate severity increases from about 4% at screening to about 10% at clinical detection.[60]

Newly diagnosed diabetics (by either screening or clinical means) rarely have retinopathy severe enough to require immediate photocoagulation. Of nearly 3,000 newly clinically diagnosed diabetics examined in the United Kingdom Prospective Diabetes Study (UKPDS), only 8 had retinopathy severe enough to require immediate photocoagulation.[57,58]

After 20 to 25 years, the great majority of all diabetics have some degree of retinopathy, but the incidence of severe retinopathy varies by baseline glycemic level. Less than 5% of those with Hb A1c levels less than 8.5% at baseline, and about 40% of those with Hb A1c greater than 11.6%, have severe retinopathy.[61-63] Today at clinical diagnosis more people are in the former category than the latter; in the UKPDS, the mean Hb A1c at clinical diagnosis was 9.3%.[64]

After 10 years' duration, about 18% of diabetics will have some degree of visual deterioration (defined as "doubling of the visual angle," eg, going from vision of 20/40 to 20/80) and 5% or less will be blind, although the absolute difference between diabetics and nondiabetics for both outcomes is not clear. People developing DM-2 after the age of 60 to 70 years have higher 10-year rates of blindness and visual deterioration, but this is also true of nondiabetics at

this age.[65] A national survey found that, compared with persons who did not have diabetes, diabetic patients (including those with recent and those with remote onset), 8% to 10% more reported "trouble seeing" and 1% to 2% reported blindness.[1]

Few studies have reported the prevalence of visual impairment among patients with DM-2 for longer than 10 years; and those that have are based on small numbers of diabetics with long-term survival who have had limited access to present-day ophthalmological techniques, including photocoagulation. The best data show that the 10-year incidence of blindness among those with DM-2 of 20 to 25 years duration is between 5% and 15%, and the 10-year incidence of visual deterioration (doubling of the visual angle) is between 35% and 45%; the higher numbers are for those diabetics requiring insulin treatment.[65]

Modeling studies extrapolating from increasing rates of retinopathy over time have estimated that nearly 20% of diabetics will eventually become blind. The highest risk is among those with onset at a younger age, who have a longer time to develop visual complications.[66,67]

Treatment to Prevent Visual Impairment

Three treatments to reduce the incidence of visual impairment have been studied: laser photocoagulation (Evidence Table 2), tight glycemic control (Evidence Table 3), and tight blood pressure control (Evidence Table 4).

Photocoagulation. For those diabetics who receive regular retinal screening, retinal photocoagulation dramatically decreases the development of severe visual impairment and blindness. Good evidence from well-performed RCTs indicates that photocoagulation for those with the worst forms of retinopathy reduces the incidence of severe visual impairment by 90%; photocoagulation for macular edema reduces the incidence of less severe visual impairment by

50%. Photocoagulation at an earlier stage of retinopathy is not as useful, making this treatment less applicable to the period between screening and clinical diagnosis.[68-70]

Tight glycemic control. Two well-performed RCTs have shown that tight glycemic control reduces the relative risk of development or progression of retinopathy by a relative 29% ($P = 0.0031$)[30] to 40% (P not given).[33] Absolute risk reduction is smaller: in the UKPDS, 10.3% of patients in the conventional glycemic control arm and 7.6% of those in the tight control group required laser photocoagulation after 10 years (absolute difference = 2.7%). Neither trial found a difference in visual outcomes. These results are similar to those of the Diabetes Control and Complications Trial among people with type 1 diabetes.[71]

Tight blood pressure control. One large (n = 1,148) well-performed RCT found that a reduction in blood pressure among hypertensive diabetics to 144/82 from 154/87 decreased the need for retinal photocoagulation by an absolute 4.1% (12.1% vs. 8.0%).[31] Such a reduction also decreased deterioration in visual acuity (defined as a reduction in visual acuity by 3 or more lines in a standardized scale) by an absolute 9.2% (19.4% vs 10.2%) over 7.5 years. About the same percentage in each group (3.3% vs. 2.4%) developed blindness.

Summary. Retinal photocoagulation is effective in reducing the incidence of visual impairment among those with severe retinopathy or macular edema. It is not of great use during the period between screening and clinical diagnosis.

Tight glycemic control reduces the development and progression of retinopathy, but the degree to which it reduces visual impairment is less clear. Any reduction in visual impairment occurs more than 10 years after the diagnosis of diabetes.[30] Even less certain is the degree to which tight glycemic control during the preclinical period between screening and clinical

detection, a time when glucose levels are at less than their peak, reduces retinopathy and later visual impairment.

Tight blood pressure control among hypertensive diabetics reduces visual impairment. Detection of DM-2 through screening could prompt tighter blood pressure control during the preclinical period. Depending on the length of the preclinical period, this practice could perhaps decrease the later emergence of vision problems related to diabetes.

Table 2 considers the number needed to screen (NNS) to prevent 1 case of blindness given various assumptions. For cases of blindness, we start with several favorable assumptions (Table 2, Case 1). Assuming that tight glycemic control yields a 29% reduction in the risk of blindness in 1 eye among diabetics identified by screening (the relative risk reduction in retinal photocoagulation in the UKPDS trial[30]), that the risk of blindness over 5 years is 1.5% (half of the 10 year risk found in UKPDS[30]), and that all newly identified diabetics achieve tight glycemic control, then the NNS is about 3,900 to prevent 1 case of blindness by tight glycemic control for 5 years. Cases 2 through 4 change the assumptions in less optimistic directions. If screening increases the percentage of newly identified diabetics with tight glycemic control by only 50% (Case 2, middle example) rather than 100% (Case 1), then the NNS becomes about 7,700. Cases 3 and 4, with even less favorable assumptions about, respectively, years of additional treatment and prevalence of undiagnosed diabetes, given higher NNS calculations.

Table 3 provides 5-year NNS calculations to prevent 1 CVD event by screening people with hypertension for diabetes. Assuming a 7.5% 5-year risk of a CVD event and a 50% relative risk reduction from tight blood pressure control, the NNS is about 500 (Table 3, Case 1). If only 50% of diabetic hypertensives detected by screening actually receive tight blood pressure control as a result of diabetes screening, the NNS is about 900 (Case 2, middle example).

Special Populations

Cross-sectional data and 1 prospective cohort study show that black diabetics have a higher prevalence and incidence of retinopathy and visual impairment than white diabetics.[59,72] Mexican American[60] and American Indian diabetics[73] also have higher rates of retinopathy than do white diabetics. If these rates translate into increased visual impairment in these groups, any benefit of screening would be larger than that for white diabetics. The NNS figures given in Table 2 for tight blood pressure control may be more favorable (ie, lower) for these groups than for white diabetics with respect to treatments to reduce visual impairment; however, the benefit of screening is as uncertain for these groups as it is for white diabetics.

Chronic Renal Failure

In some diabetics, metabolic, hemodynamic, and genetic factors interact to produce diabetic nephropathy, a condition that can progress to chronic renal failure (CRF). The hallmark of diabetic nephropathy is albuminuria. Albuminuria develops some years after the actual onset of diabetes, first in small amounts (microalbuminuria) and then larger amounts (macroalbuminuria); in some cases, it eventually progresses to CRF.

Incidence and Prevalence of Albuminuria and Chronic Renal Failure

About 18% to 20% of people with both screening and clinically detected diabetes have microalbuminuria.[74-76] The prevalence of macroalbuminuria is about 3% at screening detection and between 4% and 8% at clinical detection.[74,77]

After 20 years with diabetes, about 25% of those without initial macroalbuminuria will have developed it. The incidence depends on baseline glycemic levels.[77]

The incidence of CRF among those without macroalbuminuria at clinical diagnosis is about 0.5% after 15 years with diabetes, 3% after 20 years with diabetes, and 10% after 30 years. Among those with macroalbuminuria at DM-2 diagnosis, the incidence of CRF is about 8% after 10 years DM-2 duration and 12% after 15 years.[78]

Treatments to Prevent Chronic Renal Failure

Three treatments have been examined to reduce the incidence of CRF among diabetics: tight glycemic control (Evidence Table 3), tight blood pressure control (Evidence Table 4), and ACE inhibitors or other agents that interrupt the renin-angiotensin system, such as angiotensin receptor blockers (ARBs) (Evidence Table 4).

Tight glycemic control. Two RCTs have examined the effectiveness of tight glycemic control in reducing the development of albuminuria and CRF in those with DM-2 – one in Japanese patients[33] and the other in the United Kingdom.[30] The UKPDS also incorporated a trial of tight versus loose blood pressure control among hypertensive diabetics.[31] The studies found that both tight glycemic control and tight blood pressure control reduced the development and progression of albuminuria. Neither intervention, however, had a statistically significant effect on the incidence of CRF. After 10 years in the UKPDS trial, less than 1% of participants in either the tight or the loose glycemic control arms had developed CRF.[30]

Use of ACE inhibitors or ARBs. Three well-conducted meta-analyses[79-81] and 8 more recent RCTs[82-89] examined the effectiveness of interruption of the renin-angiotensin system in reducing albuminuria and CRF among people with DM-2. All found that either ACE inhibitors or ARBs reduced the development and progression of albuminuria, with an effect greater than that for other antihypertensives. Two of these studies, both involving diabetics with macroalbuminuria, found a reduction in CRF in patients taking ARBs compared with

placebo.[83,84] In the other trials, the number of participants developing CRF over the time of the trials was low.

One RCT among people with type 1 diabetes reported a decrease in CRF among those receiving ACE inhibitors.[90] A meta-analysis of RCTs among nondiabetics with proteinuric renal disease reported similar findings.[91]

Summary. Few people have macroalbuminuria at either screening or clinical diagnosis. Among the great majority without macroalbuminuria, CRF is rare for more than 15 years. Tight glycemic and blood pressure control and use of ACE inhibitors or ARBs reduce the development and progression of albuminuria; ARBs can reduce CRF among diabetics with macroalbuminuria. Whether any of these treatments, if started between screening and clinical diagnosis, which is a time when few diabetics have albuminuria, would have an important impact on the long-term incidence of CRF remains uncertain.

Special Populations

More than 15 studies have consistently found that diabetic American Indians, blacks, and Hispanics in the United States have more than twice the incidence of macroalbuminuria and CRF that diabetic whites have.[92] A higher rate of CRF would potentially mean a higher benefit from screening for these groups compared with white diabetics. The benefit of screening (ie, starting treatment at screening compared with clinical diagnosis), however, is as uncertain for these groups as it is for white diabetics.

Lower Extremity Amputations

Diabetes affects the lower extremities in 2 main ways. Diabetes affects peripheral nerves, causing pain and loss of sensation; it also promotes the development of peripheral vascular disease, thereby decreasing the ability to heal ulcers and fight infections in the feet. The loss of sensation and decreased vascular supply lead to foot ulcers and infections, which lead to amputation.

Incidence and Prevalence

We sought data on the incidence and prevalence of diabetic distal sensory neuropathy (DSN), peripheral vascular disease (PVD), foot ulcers, and lower extremity amputation (LEA). No study provided evidence about the prevalence of any of these conditions at the time DM-2 would be detected by screening.

At clinical diagnosis, from 7%[93] to 17%[94] of diabetics have symptomatic DSN, and from 8%[95] to 13%[57] have lost one or more pulses in their feet. Ten years after clinical diagnosis, between 17% and 25% of people with DM-2 will have DSN from diabetes. Incidence varies with higher baseline levels of glycemia.[61,93,96]

No study provided information about the incidence or prevalence of foot ulcers after clinical diagnosis of diabetes; we assume that prevalence is low. Two studies of people with DM-2 of both short and long duration found an incidence of foot ulcers of 5% to 7% after 1 to 3 years of follow-up.[97,98] Other studies estimate that about 15% of all diabetics will develop at least 1 foot ulcer during their lifetimes.[6] A large historical cohort study found that about 15% of those with foot ulcers required some level of amputation over 3 years of follow-up.[97]

We uncovered no information on LEA prevalence at clinical diagnosis. One prospective and 1 historical cohort study found that the 20- to 25-year cumulative incidence of LEA is between 3% and 11%.[7,99] This includes all types of LEA, about three-quarters of which are below the knee or lower.[7] In the UKPDS cohort, between 1% and 2% of participants had had an amputation within 10 years. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) population-based cohort, about 7% of those with short duration DM-2 had had an amputation within 14 years.[100]

Treatments to Prevent Lower Extremity Amputation

Three types of treatments have been tested to reduce LEA: tight glycemic control (Evidence Table 3), tight blood pressure control (Evidence Table 4), and foot care programs (Evidence Table 5).

Tight glycemic and blood pressure control. The UKPDS tested the efficacy of tight glycemic[30] and blood pressure control[31] on LEA. Although the UKPDS reported a trend toward a lower incidence of amputations with both tight glycemic control and tight blood pressure control, the differences did not attain statistical significance ($P = 0.099$ for tight glycemic control and $P = 0.17$ for tight blood pressure control). Because the incidence of LEA was so low, the absolute differences were also low (0.6% difference for tight glycemic control and 1.3% for tight blood pressure control).

Foot care programs. A recent well-conducted systematic review examined the efficacy of foot care programs on the incidence of foot ulcers and amputations.[101] Many of the studies had flaws such as too few participants or too brief an intervention. Two well-conducted trials have been reported: 1 in a primary care setting and the other of diabetics at high risk of foot ulcers. They found that intensive programs including patient education, special shoes, and health

care interventions can reduce the incidence of both foot ulcers and LEAs by as much as 60%.[102,103]

Summary. In the first 10 years after the onset of DM-2, the incidence of LEA is low. LEA in diabetics occurs primarily as a later complication, related to the development of DSN and PVD, which themselves take time to develop. Although foot care programs, and perhaps tight glycemic and blood pressure control, may reduce LEA over the long term, it is not clear that implementation of these interventions during the time between screening and clinical detection would have a large impact on the later development of LEA.

Special Populations

At least 2 well-conducted cohort studies[99,104] and 2 cross-sectional studies[105-107] found that the incidence of LEA is greater among black and American Indian diabetics than among non-Hispanic white diabetics. The data are less clear for other ethnic groups. Although the incidence of LEA is higher in these groups, the benefit of treatment between screening and clinical detection is as uncertain as it is for white diabetics.

Cardiovascular Events

Many studies establish DM-2 as an important risk factor for CVD events, including myocardial infarction (MI) and thromboembolic stroke (cerebrovascular accident [CVA]). Although glucose may itself have some vascular toxicity, some of the increased CVD risk experienced by diabetics can be attributed to the association of DM-2 and IFG/IGT with traditional risk factors such as hypertension and dyslipidemia. New CVD risk factors (eg, small, dense low-density lipoprotein (LDL) particles, apolipoproteins (a) and (b), homocysteine,

insulin, and both impaired fibrinolysis and hypercoagulability), as well as yet-undiscovered risk factors, may also contribute to the increased risk of those with DM-2. Thus, DM-2 is both an independent risk factor for CVD and also a marker of increased CVD risk from other risk factors.

Incidence and Prevalence of CVD Events

The absolute prevalence of established CVD at screening or clinical diagnosis of DM-2 ranges from 8% to 23% depending on the presence of other CVD risk factors. . The prevalence is 3% to 12% higher than among similar nondiabetics; people with IFG/IGT have an intermediate prevalence between diabetics and nondiabetics.

At least 14 prospective cohort studies have found that the risk of CVD events in diabetic men is about twice that in nondiabetics, even after adjusting for age, hypertension, dyslipidemia, and smoking.[8-16,18-21,108] For women, the adjusted CVD risk among diabetics is perhaps fourfold that in nondiabetics.

The absolute excess CVD risk for diabetics compared with nondiabetics depends on the number of other CVD risk factors. It ranges from less than 5% over 10 years for those with few additional risk factors to 15% or more for those with several additional risk factors. The absolute excess CVD risk for those with IFG/IGT is about half that of people with DM-2, although whether this excess risk is independent of other risk factors is not clear.

The UKPDS provided information about the absolute CVD risk among a population-based cohort of newly clinically diagnosed diabetics.[30] After excluding people with recent MI and current angina or congestive heart failure (CHF), the investigators found that between 14% and 18% of all other diabetics (median age, 53 years) had suffered an MI within 10 years, and

that 5% to 6% had suffered a stroke. Between 10% and 12% had died from diabetes-related causes, primarily CVD events.

Treatment to Prevent CVD Events

Three treatments to reduce the incidence of CVD events among diabetics have been studied with high-quality RCTs: tight glycemic control (Evidence Table 3), tight blood pressure control (Evidence Table 4), and treatment of dyslipidemia (Evidence Table 6).

Tight glycemic control. To date, no RCT has demonstrated a statistically significant reduction in CVD events from tight glycemic control.[30,109,110] The UKPDS reported 3 key findings: (1) a reduction in both fatal and nonfatal MI (16.3% to 14.2%, for a relative risk [RR] of 0.84) of borderline statistical significance ($P = 0.052$); (2) a reduction in sudden death (1.6% to 0.9%, RR = 0.54, $P = 0.047$, with a P value of ≤ 0.01 required for statistical significance); and (3) no reductions in stroke (RR = 1.11, $P = 0.52$), heart failure (RR = 0.91, $P = 0.52$), or angina (RR = 1.02, $P = 0.91$).[30]

Tight blood pressure control. Nine recent RCTs have examined various aspects of the treatment of hypertension among people with DM-2. As a whole, they have shown that:

- An aggressive approach to blood pressure control among diabetics reduces CVD events by a relative 50% or more. In the Hypertension Optimal Treatment trial, the absolute risk reduction was 24.4 vs 11.9 events per 1,000 patient-years, $P = 0.005$; the number needed to treat (NNT) for 3.8 years was 80. The target blood pressure should be even lower than that for nondiabetics.[31,32]

- Treatment of isolated systolic hypertension among older diabetics reduces CVD events by a relative 34% to 69%.[111,112]

- Treatment of diabetics with at least 1 other CVD risk factor (whether or not they have hypertension) with ramipril reduces CVD events by a relative 22% and all-cause mortality by a relative 16%.[34]

- ACE inhibitors may reduce CVD events more than other antihypertensives,[113-115] although 1 trial found no difference between treatment with an ACE inhibitor and a

beta blocker.[87] A more recent study found that diabetics (but not nondiabetics) achieved more benefit from an ARB than a beta blocker.[116,117]

Lipid control. Four secondary prevention trials of treating lipids had enough diabetics to permit subgroup analyses. Three used HMG co-A reductase inhibitors (statins);[118-121] 1 tested gemfibrozil.[122] In each case, lipid treatment reduced the incidence of coronary heart disease (CHD) events by about the same relative percentage among diabetics as among nondiabetics and those with IFG/IGT. The relative risk reduction ranged between 19% and 42%. In a pooled study of the results of 2 secondary prevention trials[120,121] that used the same drug (pravastatin) found that, among participants with an initial LDL level of 125 mg/dl or less, diabetics had a greater benefit from pravastatin treatment than nondiabetics.[123]

No primary prevention trial of lipid therapy has included sufficient numbers of diabetics to perform reliable analyses, although trends in these trials are also in the direction of benefit.[124] In a small primary prevention trial, Elkeles et al found a statistically significant 16% absolute reduction in definite CHD events (an endpoint combining MI and ischemia) between diabetics assigned to bezafibrate and those given placebo.[125]

Aspirin treatment also reduces CHD events among people with diabetes to the same degree as among nondiabetics.[126-128]

Summary. The absolute incidence of CVD events among newly clinically diagnosed diabetics is more than 15% after 10 years, higher for those with additional risk factors and lower for those with fewer risk factors. This rate is substantially higher than the rate for nondiabetics at the same risk factor level. Whether tight glycemic control will lower this incidence is not clear.

Some evidence suggests that tight blood pressure control with a target diastolic pressure of 80 mm Hg, probably using an ACE inhibitor or an ARB, reduces event rates by approximately a relative 50%. Further, knowing whether a person has diabetes is important in

determining CHD risk. Treating persons at higher CHD risk, including diabetics, for dyslipidemia is both effective and cost-effective.[129]

Table 3 provides 5-year NNS calculations to prevent 1 CVD event by screening people with hypertension for diabetes. Assuming a 7.5% 5-year risk of a CVD event and a 50% relative risk reduction from tight blood pressure control, the NNS is about 500 (Table 3, Case 1). If only 50% of diabetic hypertensives detected by screening actually receive tight blood pressure control as a result of diabetes screening, the NNS is about 900 (Case 2, middle example).

Even with less optimistic assumptions (Cases 3 and 4), the NNS calculations for preventing 1 CVD event are still lower than those for preventing blindness in 1 eye (from Table 2). Moreover, the initial assumptions for the CVD calculations are more secure and based less on extrapolation than those in the blindness example.

Special Populations

Data are not clear about the relative prevalence and incidence of CVD in diabetic black, Hispanic, and American Indian groups compared with diabetic non-Hispanic whites.[130] Some American Indian groups may have lower incidence, but other American Indian groups may have higher incidence.[131,132] Thus, no clear evidence exists at present to alter conclusions about screening to reduce CVD events because of membership in one of these population groups.

Early Treatment of Impaired Fasting Glucose/Impaired Glucose Tolerance

Several observational studies have shown that people who develop DM-2 have potentially modifiable risk factors such as obesity and reduced physical activity.[133-140] This has led clinicians to wonder whether lifestyle interventions at the IFG/IGT stage might reduce the

incidence of DM-2 and thereby lower diabetes complications. If lifestyle modification (weight management, increased physical activity) in persons with IFG/IGT can reduce the progression to DM-2, an additional argument for screening would be to detect persons at this stage who could benefit from interventions. A potentially large group might benefit; NHANES III found that 6.9% of adults ages 20 and older met criteria for IFG and 15.8% met criteria for IGT. What is unclear is whether lifestyle interventions in this group are effective.

Three well-conducted RCTs of lifestyle interventions have been reported (Evidence Table 7).[141-143] A large 6-year study from China (the Da Qing trial) reported a 20% absolute reduction in progression from IGT to DM-2.[141] Two large RCTs are most relevant for this discussion. One from Finland found that an intensive lifestyle change program reduced the development of DM-2 by 58% over 3.2 years.[143] A similar trial in the United States found the same relative risk reduction from an intensive lifestyle change program; in a group assigned to the drug metformin, the relative risk reduction was 31%.[142] A small RCT (with appreciable attrition) from the United Kingdom found no change in lifestyle and no change in progression to DM-2.[144]

Two other RCTs have found that ACE inhibitors reduced the development of DM-2 in populations at increased CVD risk;[89,145] another found the same result in hypertensive patients.[113] The absolute reductions were small: 0.8% in one trial and 1.6% in the other. Two other trials found small reductions in the incidence of DM-2 among people taking losartan (an ARB) compared with atenolol (a beta blocker)[116] and among people with high CVD risk taking pravastatin compared with placebo.[146] A drug trial of acarbose to reduce the progression from IGT to DM-2 is in progress.[147]

In summary, lifestyle modification and/or drugs can reduce the incidence of DM-2, although the degree to which this reduces diabetic complications (i.e., health outcomes) is uncertain. The cost-effectiveness of intensive lifestyle change programs is also untested.

Harms of Screening and Treatment

Screening for DM-2 could cause harm in at least 2 ways. One is by labeling people unnecessarily, thus causing anxiety and a change in self-perception. Another is by subjecting people to a potentially harmful treatment for a longer time.

We found no studies of the psychological effects of being diagnosed with diabetes by screening. Nevertheless, adverse effects of labeling remain a potential problem. For example, false-positive screening tests could contribute to psychological distress. [50,148-152] In addition, between 30% and 50% of those labeled as having IGT will revert to normal glycemia without developing DM-2.[153-159]

On the whole, treatments for diabetes are relatively safe (Evidence Table 8). Tight glycemic control at a time when glycemic levels are relatively low (ie,, the time between screening and clinical diagnosis) can induce hypoglycemia; in the UKPDS, 2.3% of people on insulin suffered a major hypoglycemic episode each year, as did 0.4% to 0.6% of those on oral hypoglycemics.[30] ACE inhibitors[160] and statins[161,162] have reasonably low levels of serious adverse effects.

The impact of diabetes treatment on quality of life has been a concern. Three RCTs indicate, however, that better glycemic control actually improves quality of life.[30,163-165]

In short, despite the potential for newly screen-detected diabetics to be harmed by labeling or earlier treatment (or both), the magnitude of this problem is unclear. Among those

who have symptomatic hyperglycemia, which may include few people detected by screening, better glycemic control improves quality of life.

Costs and Cost-Effectiveness of Screening and Earlier Treatment

In a clinically diagnosed group of diabetics, diabetes-associated incremental costs are evident from the first year and may average $2,000 to $3,000 per person annually.[166] Intensive treatment will cost more.[167] Cardiovascular and renal complications increase costs by a factor of 3 to 7[168] (Evidence Table 9).

We found 1 modeling study of the cost-effectiveness of screening for DM-2 in the United States.[167] The model assumed that screening allows an additional 5.5 years of tight glycemic control and that the effect of this treatment would be seen only in reduction of eye, kidney, and lower extremity complications. The risk of these complications was taken from the body of literature reviewed in this systematic review; risk reduction was extrapolated from the major study of glycemic control for type 1 diabetics.[71] Glycemic control after diagnosis in both screened and unscreened modeling groups was assumed to be similar to the level for the UKPDS diet-control group rather than the level for the intensive-control group.

The cost-effectiveness of one-time screening varied by age and ethnic group. Cost per quality-adjusted life year (QALY) gained for persons ages 25 to 34 was $13,376 for whites and $822 for African Americans; for persons in the age range 55 to 64 years, the figures were $116,908 for whites and $70,759 for African Americans. This differential by age reflects the extrapolation that tight glycemic control needs to be applied for some years before it reduces visual impairment or CRF. Sensitivity analyses found that cost-effectiveness ratios triple if the

preclinical period is cut in half or if intensive rather than loose glycemic control is instituted at diagnosis.

The prevalence of undiagnosed DM-2 is low in younger age groups (eg, 0.6% of those ages 20 to 39 years).[25] For this reason, a strategy of screening younger people would detect relatively few of the people destined eventually to develop DM-2.

Diabetes care, especially intensive glycemic control and the care of complications, is expensive. According to one modeling study, screening younger people was more cost-effective than screening older people, and screening African Americans was more cost-effective than screening whites. This study extrapolated benefits from studies showing that tight glycemic control effectively reduces intermediate outcomes (eg, retinopathy and albuminuria) rather than health outcomes (eg, severe vision impairment and CRF). It also found that if the preclinical period were shorter than assumed, or if intensive glycemic control were instituted at diagnosis (whether screening or clinical), then cost-effectiveness would be considerably worse. Finally, this study did not consider any benefits of earlier, more intensive treatment of CVD risk factors.

Chapter 4. Discussion

Effects of Screening

The benefits of screening for type 2 diabetes mellitus (DM-2) have not been demonstrated in any well-performed randomized controlled trial (RCT). Indirect evidence indicates that diabetic complications such as blindness, chronic renal failure (CRF), and lower extremity amputation (LEA) are relatively uncommon until diabetes has been present for 15 to 20 years. The effect on these distant outcomes of an additional few years of tight glycemic control during the period between a screening diagnosis and a clinical diagnosis is uncertain. The incremental benefit of systematic screening is further mitigated by the prevalence of haphazard screening. Systematic screening poses some potential but unproven harm. The costs of screening and earlier treatment and the efforts required of primary care providers are substantial.

In the decade after the diagnosis of DM-2, diabetic outcomes such as visual impairment less severe than blindness and cardiovascular disease (CVD) events are more common than the complications noted above. Visual impairment and CVD events can be reduced by a clinically important amount among hypertensive diabetics by tight control of blood pressure, using a target diastolic blood pressure of 80 mm Hg and ACE inhibitors as a first line of therapy.

Three factors are significant in understanding the impact of screening and estimating numbers needed to screen (NNS): extent to which diabetics with hypertension attain optimal blood pressure control, length of any preclinical period, and prevalence of undetected diabetes among hypertensives. That is, all other things equal, estimates of the NNSs to prevent either 1

case of visual impairment or 1 CVD event will be lower if knowledge of the diagnosis of DM-2 substantially increases the percentage of hypertensive diabetics with optimal blood pressure control, if the detectable preclinical period is 5 years or more, or if the prevalence of undiagnosed DM-2 among those with blood pressure of 140/90 or greater is about 6% (or if any combination of these factors holds).

A similar analysis might be made for other CVD risk factors. If detection of DM-2 improves CVD risk assessment and increases the number of people appropriately treated for dyslipidemia, if it increases the effectiveness of treatment for tobacco use, or if it increases the number of people appropriately treated with prophylactic aspirin, then this earlier diagnosis would add to the benefits of screening. No direct evidence permits one to estimate the degree to which detection of DM-2 would lead to these types of improved treatment.

If treatment of people with IFG/IGT not only prevents the development of DM-2 but also has a large effect on its complications, or if knowledge of the presence of IFG/IGT improves optimal treatment of CVD risk factors among this large group, then these would be added benefits of screening. However, we do not yet have full enough understanding of these issues to base widespread action on them.

Recommendations for Further Research

Screening for DM-2 is an important issue with many unanswered questions. Although several treatments started at clinical diagnosis are known to reduce diabetic complications, the extent to which they have added effect by earlier initiation, during the period between screening and clinical detection, is unknown. Studies are needed that examine the optimal starting time, including the preclinical period, of various treatments in preventing complications. Because

some of these complications occur only many years after diagnosis, these studies should include long-term follow-up.

Because not all people with abnormal glycemic tests are at equal risk of diabetic complications, studies that help define high- and low-risk groups are needed to better target such interventions as screening.

Ideally, an RCT should be considered. Mounting such a study, although expensive and difficult, could teach us much about preventing diabetic complications. In the absence of such a trial, natural experiments should be examined. Areas that adopt an aggressive screening strategy could be compared with areas that include little screening. Registries of people with diabetes, including diabetic complications, would be helpful in these studies.

Until we have better evidence about the benefits, harms, and costs of screening, its role in the effort to reduce the burden of suffering of diabetes will remain uncertain. Current evidence suggests that the benefits of screening are more likely to come from modifications of CVD risk factors than from tight glycemic control.

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Acknowledgments

This study was developed by the Research Triangle Institute—University of North Carolina Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (Contract No. 290-97-0011), Rockville, Maryland.

We thank David Atkins, MD, MPH, Chief Medical Officer for the Center for Practice and Technology Assessment, and Jean Slutsky, PA, MSPH, the project officer for this project, both at the Agency for Healthcare Research and Quality, for their assistance throughout the project. We are especially indebted to Loraine Monroe of RTI International for superior word processing support. We also acknowledge Warren Newton, MD, and Eric Baggstrom, MD, both of the University of North Carolina at Chapel Hill, for their assistance early in the project.

In addition, we would like to thank our current US Preventive Services Task Force topic liaisons, Paul Frame, MD, of Tri-County Family Medicine, Cochocton, NY, and Steven Woolf, MD, MPH, of Virginia Commonwealth University, Fairfax, VA, for their guidance during this project. We would also like to thank Harold C. Sox, Jr., MD, of the *Annals of Internal Medicine*, Philadelphia, PA, and formerly of the US Preventive Services Task Force, for his assistance and guidance early in the project.

An earlier version of this systematic review underwent extensive external peer review in 2000. We thank the following peer reviewers for helpful comments and suggestions: Amanda Adler, MD, PhD, Radcliffe Infirmary, Oxford, England; Elizabeth Barrett-Connor, MD, University of California San Diego, La Jolla, CA; Tom Elasy, MD, Vanderbilt University,

Nashville, TN; Denice Feig, MD, MSc, FRCPC, Mount Sinai Hospital, Toronto, Onatario; R.A. Hayward, MD, University of Michigan, Ann Arbor, MI; Richard Kahn, PhD, American Diabetes Association, Alexandria, VA; Vincenza Snow, MD, American College of Physicians-American Society of Internal Medicine, Philadelphia, PA; Stephen Spann, MD, Baylor College of Medicine, Houston, TX; and Eric Vogel, MD, MCP, Hahnemann University, Philadelphia, PA.

Evidence Table 1. Properties and Yield of Screening Tests

Source Author, Year	Study Population	Measurements	Results	Comments Quality
Olefsky JM et al., 1974[50]	N: 31 (adult volunteers)	FPG 2-hour PG (each repeated for each participant, 48 hours apart)	9 of 31: FPG deviated by > 10%, but none by > 30% 17 of 31: 2-hour PG deviated by > 10% and 3 deviated by > 30%	Greater variability in 2-hour PG than in FPG Quality: Fair
Blunt BA, et al., 1991[48]	N: 1,851 men and women Design: Cross-sectional, population-based	FPG 2-hour PG	For gold standard of 2-hour PG ≥ 200 mg/dl: FPG, cutpoint 121 mg/dl Sensitivity: 65.6% (ages 50-64) Sensitivity: 40% (ages 65-70) Specificity:> 95% (both ages)	FPG less sensitive for detecting 2-hour PG ≥ 200 mg/dl in older age groups Quality: Good
McCance DR, et al., 1995[171]	N : 960 Pima Indians Ages : 25+ Design : Cross-sectional and longitudinal Not receiving drugs for diabetes	FPG 2-hour PG Hb A1c Direct opthalmoscopy through dilated pupils	For detecting retinopathy: FPG, cutpoint 122 mg/dl Sensitivity: 81.2% Specificity: 77.1% 2-hour PG, cutpoint 200 mg/dl Sensitivity: 87.5% Specificity: 75.8% HbA1c, cutpoint 6.1% Sensitivity: 81.3% Specificity: 76.8%	Also found threshold for predicting 5-year incidence of retinopathy Quality: Good
Mooy JM, et al., 1996[150]	N: 246 (with NGT), 198 (with IGT), 80 (with new-DM) Ages: 50-74 Design: Hoorn Study, population-based, prospective cohort	Repeated FPG and 2-hour PG in same individuals	Intra-individual variation: [standard deviation of test-retest difference (mg/dl)]: FPG / 2-hour PG NGT 7.2 / 23.4 IGT 9.0 / 32.4 New-DM 12.6 / 41.4	Variation greater for 2-hour PG than for FPG Variation greater for new-DM and IGT than for NGT Quality: Good

Evidence Table 1. Properties and Yield of Screening Tests (continued)

Source Author, Year	Study Population	Measurements	Results	Comments Quality
Engelgau MM, et al., 1997[41]	N: 1,018 Egyptians Ages: 20+ Design: Cross-sectional, population-based Examination of people with capillary blood glucose > 100 mg/dl, diabetic and nondiabetic	FPG 2-hour PG Hb A1c Retinal photograph	For detecting retinopathy (excludes those with diabetes): FPG, cutpoint 125 mg/dl Sensitivity: 84% Specificity: 77% 2-hour PG, cutpoint 200 mg/dl Sensitivity: 86% Specificity: 78% Hb A1c, cutpoint 6.4% Sensitivity: 80% Specificity: 74%	ROC curves very similar for all 3 tests 30 % non-response Quality: Fair
Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997[42]	N: 2,821 Ages: 40-74 Design: NHANES III, cross-sectional	FPG 2-hour PG Hb A1c Retinal photograph	Exact sensitivity and specificity not given All 3 tests very similar by graph	Personal communi-cation in another report Quality: Fair

Evidence Table 1. Properties and Yield of Screening Tests (continued)

Source Author, Year	Study Population	Measurements	Results	Comments Quality
Harris MI et al., 1997[29]	N: 2,844 (no diagnosed diabetes) Ages: 40-74 Design: NHANES III, cross-sectional, population-based	FPG 2-hour PG	For 2-hour PG ≥ 200 mg/dl as reference standard for diagnosing diabetes, probability of diabetes given following FPG: ≥ 140 mg/dl=91% 126-139 mg/dl=47% 110-125 mg/dl=18% <110 mg/dl =1.6%	2-hour PG ≥ 200 classifies more people as diabetic than FPG ≥ 126 mg/dl 2-hour PG 140-199 classifies more people as IGT than FPG 110-125 classifies as IFG Quality: Good
Bjornholt JV, et al., 1999[44]	N: 1,973 (healthy nondiabetic men) Ages: 40-59 Design: Population-based, prospective cohort (22 years followup)	Fasting blood glucose	Men in highest fasting blood glucose quartile (≥ 85 mg/dl) had higher CVD mortality than those in lower three quartiles, independent of major CVD risk factors, (RR=1.4 [1.04-1.8]) Non-CVD deaths were unrelated to blood glucose	Quality: Good
Coutinho M, et al., 1999[43]	N: 20 studies including 95,783 persons followed an average of 12.4 years Design: Meta-regression analysis All persons nondiabetics	FPG 2-hour PG	Exponential relationship between either FPG or 2-hour PG and CVD events beginning far below diabetes cutpoint	Could not adjust for other CVD risk factors, thus uncertain if CVD risk is independent Quality: Fair

Evidence Table 1. Properties and Yield of Screening Tests (continued)

Source Author, Year	Study Population	Measurements	Results	Comments Quality
Khaw KT, et al., 2001[47]	N: 4,662 men Ages: 45-79 Design: Population-based, prospective cohort (2-4 year followup)	Hb A1c CVD events CVD Mortality All-cause mortality	Hb A1c continuously associated with all-cause and CVD mortality throughout the entire population distribution of Hb A1c down to 5% Increase of 1% in Hb A1c associated with a 28% increase in risk of death independent of other CVD risk factors	Quality: Good
Rolka DB, et al., 2001[54]	N: 1,471 volunteers Ages: 20+ Design: Cross-sectional Recruited during routine health center visits and at community health fairs	FPG 2-hour PG Random capillary blood glucose ADA screening questionnaire (7 items)	For detecting either FPG ≥ 126 or 2-hour PG ≥ 200 mg/dl: CBG (≥ 120 mg/dl) Sensitivity: 75% Specificity: 88%	Questionnaire much less sensitive Quality: Fair
Saydah SH, et al., 2001[46]	N: 3,174 adults Ages: 30-75 Design: NHANES II followup study, prospective cohort (12-16 years followup)	FPG 2-hour PG All-cause mortality CVD mortality	Using normal glucose tolerance as referent group: Multivariate adjusted RR for all-cause mortality: - Abnormal glucose tolerance: 1.42 (1.08=1.87) - Undiagnosed diabetes: 1.77 (1.13-2.75) - Diagnosed diabetes: 2.11 (1.56-2.84) - (Similar trend for CVD mortality)	FPG and 2-hour PG both used in constructing categories Quality: Good

Evidence Table 2. Studies of Laser Photocoagulation

Source: Author, Year	Study Population: Selection/ Randomization	Study Population: Description	Time Frame	Interventions/ Co-Interventions	Measurements: Exposures and Outcomes
The Diabetic Retinopathy Study Research Group, 1981[172]	Selection: Clinic-based multi-center trial; US Randomization: One eye randomly assigned to photocoagulation and the other eye no treatment Inclusion: Severe non-proliferative diabetic retinop. in both eyes or PDR in one eye and visual acuity of 20/100 or better in each eye	Baseline: 1,742 1-yr f/u: 1,624 3-yr f/u: 1,187 5-yr f/u: 519 Age: 20-29 yrs: 23% 30-39 yrs: 17% 40-49 yrs: 18% 50-59 yrs: 27% Gender: Male: 56% Ethnicity: White: 94%	Start: 1971 F/u: 1976 5-yr f/u	Interventions: Photocoagulation: xenon arc and argon laser (direct and scatter)	Exposures: Diabetes mellitus with varying degrees of retinopathy Outcomes: Severe visual loss: visual acuity <5/200 at 2 consecutive visits (inability to read top line of Snellen chart at distance of 5 feet) Measurements: Fundus photographs graded according to modified Airlie House Classification scheme, Snellen chart Blinding: Visual acuity measured by masked examiners
Early Treatment Diabetic Retinopathy Study, 1985,[173] 1987,[69] 1991[174]	Selection: Clinic-based multi-center trial Randomization: One eye randomly assigned to immediate photocoagulation and the other eye to deferral Inclusion: Mild-to severe nonproliferative retinop. or early PDR with or without diabetic macular edema	Baseline: 3,711 1-yr f/u: 3,600 3-yr f/u: 3,300 5-yr f/u: 2,200 Age: < 50 yrs: 48% > 50 yrs: 52% Gender: Male: 56% Ethnicity: White: 76%	Start: 1980-1985 F/u: 1990 5-yr f/u	Interventions: Photocoagulation: immediate and deferred	Exposures: Diabetes mellitus with varying degrees of retinopathy Outcomes: Moderate visual loss: loss of 15 or more letters (3 or more lines) on the visual acuity chart Severe visual loss: visual acuity <5/200 at 2 consecutive visits Measurements: Fluoroscein angiograms, fundus photographs graded according to modified Airlie House Classification scheme, and best-corrected visual acuity Blinding: Masked treatment assignment

Evidence Table 2. Studies of Laser Photocoagulation (continued)

Attrition: Loss to Follow-Up	Results	Conclusions	Comments/ Quality Issues
Loss to f/u: None	Intention to Treat: Cumulative Incidence of severe visual loss in eyes with severe retinopathy 3-yr f/u 5-yr f/u Treated: 9% 13% Control: 21% 32% *P* < .001	This 5-yr study demonstrated a 50% reduction in severe visual loss in eyes with severe retinopathy treated with photocoagulation	Limitations: Clinic-based Comments (Harms): Decrease in visual field in 25% xenon-treated eyes vs. 5% argon-treated Decrease in visual acuity of two or more lines: 11% xenon-treated eyes; 3% argon-treated eyes. Also, some decrease in dark adaptation Quality: Good
Loss to f/u: 164 lost to f/u, 706 died, 34 vital status unknown	Intention to Treat: Cumulative incidence of severe visual loss 5-yr f/u: Early photocoag 2.6% Deferral of photocoag 3.7% (NS) (For patients with only mild-moderate nonproliferative retinopathy, rates of severe visual loss were even lower) 3-yr f/u: Cumulative incidence of loss of visual acuity (doubling of visual angle) in eyes with mild-moderate nonproliferative retinopathy and macular edema: Immediate tx: 12% Deferred tx: 30%	For eyes with mild to moderate nonproliferative retinopathy treated with early photocoagulation, the rates of severe visual loss were low and were not significantly different from the deferred eyes Any reductions in the incidence of visual loss were not sufficient enough to compensate for side effects of early photocoagulation Immediate photocoagulation best for eyes with macular edema that involves or threatens the center of the macula	Limitations: Clinic-based Comments: Embedded aspirin component showed no eye benefit, but reduced CVD events by 17% Quality: Good

Appendix B Evidence Table 3: Studies of Tight Glycemic Control

Study Population (Quality)	Study Years	Groups N	Glycemic Control	Renal Failure	Severe Visual Impairment	Myocardial Infarction	Stroke	Amputation	All-Cause Mortality
UGDP, 1971[175]; 1978 [176] (fair)	8.75				Acuity ≤ 20/200 either eye	Significant ECG abnormality			
		Placebo: 204	22.8% increase**	NR	11.2%	20%	NR	1.5%	26.3%
		Insulin variable: 198	13.5% decrease**		11.4% (NS)	17.6% (NS)		1.6% (NS)	24.0% (NS)
UKPDS 33, 1998 [169] (good)	10				Vision too poor to drive				
		Conventional: 1,138	7.9%†	< 1% (*P* = 0.45)	11%	16.3% (*P* = 0.052)	4.8% (*P* = 0.52)	1.6% (*P* = 0.15)	18.7% (p=0.44)
		Intensive: 2,729	7.0%†	< 1%	11%	14.2%	5.4%	1.1%	17.9%
UKPDS 34, 1998 [177] (good)*	10.7				Blind in one eye				
		Conventional: 411 (primarily diet)	8.0%†	< 1% (*P* = 0.90)	3.2% (*P* = 0.87)	17.8%	5.6%	2.2% (*P* = 0.57)	21.7%
		Intensive: 342 (metformin)	7.4%†	< 1%	3.5%	11.4%	3.5%	1.8%	14.6%
Kumamoto, 1995 [178]; 2000 [179] (fair)	6					Major CVD event			
		Conventional: 50	9.4%†	NR	NR	1.3 events/100 p-y			NR
		Intensive: 52	7.1%†			0.6 events/100 p-y (NS)			
VA CSDM, 1997 [180]; 1995 [181]; 1999 [182]; 2000 [183] (fair)	2.25				Unilateral or bilateral visual impairment				
		Standard group: 78	9.2%†	NR	9%	5.1%	2.6%	0	5.1%
		Intensive group: 75	7.1%†		6.7% (NS)	6.7% (NS)	6.7% (NS)	1.3% (NS)	6.7% (NS)
Steno 2, 1999 [184] (fair)	3.8				Blind in one eye	Nonfatal	Nonfatal		
		Standard: 80	9.0%†	0	9.0%	5.1%	10.2%	5.1%	2.6%
		Intensive: 80	7.6%†	0	1.3% (*P* = 0.03)	5.2% (NS)	1.3% (NS)	5.2% (NS)	5.2% (NS)

NR = Not reported
** = change in fasting blood glucose from baseline
† = Median hemoglobin A1C
UGDP= University Group Diabetes Program
UKPDS= UK Prospective Diabetes Study Group
Steno = Steno type 2 randomized study
VA CSDM = VA Cooperative Study on Glycemic Control and Complication in Type 2 Diabetes

Appendix B Evidence Table 4. Studies of Antihypertensive, ACE Inhibitors and ARB Medications

Study Population	Study Years Age	Groups N	BP Control	MI	Stroke	CVD Events Mortality	Non-CVD Outcomes	Adherence Withdrawal	Blinding Comments Quality
Estacio et al., 1998 [185] ABCD	5 57	Nisoldipine 235 Enalapril 235	135/82 135/82	10.6% 2.1% *P* = 0.001	4.7% 3.0% NS	<u>CVD death:</u> 4.3% 2.1% NS	No difference vision, ESRD	<u>D/C study drug:</u> 39.1 % 34.9%	Double-blind MI a secondary endpoint <u>Quality</u>: Fair
Hansson et al., 1998[170] HOT	3.8 61.5	≤ 90** 501 ≤ 85 501 ≥ 80 499	144/85 141/83 140/81	7.5* 4.3 3.7 *P* = 0.11	9.1 7.0 6.4 *P* = 0.34	<u>CVD mortality*:</u> 11.1 11.2 3.7 *P* = 0.016	NR	<u>% DBP > 90:</u> 12% 7% 6% 2.6% study withdrawal	Open label <u>Quality</u>: Fair
Tatti et al., 1998 [186] FACET	2.8 62-63	Fosinopril 189 Amlodipine 191	157/88 153/86	1.8% 2.4% *P* = 0.1	0.7% 1.9% *P* >0.1	<u>Major CVD event:</u> 2.6% 5.0% *P* = 0.03	NR	<u>D/C study drug:</u> 19.0% 27.2%	Open Label <u>Quality</u>: Fair

Appendix B Evidence Table 4. Studies of Antihypertensive, ACE Inhibitors and ARB Medications (continued)

Study Population	Study Years Age	Groups N	BP Control	MI	Stroke	CVD Events Mortality	Non-CVD Outcomes	Adherence Withdrawal	Blinding Comments Quality
UKPDS-38, 1998[187]	8.4 56-57	Less tight 390 Tight 758	154/87 144/82	23.5 18.6* *P* = 0.13	11.6 6.5* *P* = 0.013	<u>DM related death:</u> 20.3 13.7* *P* = 0.019	<u>ESRD:</u> 2.3 1.4* *P* = 0.29 <u>Vision:</u> 19.4% 10.2% *P* = 0.004	No drug 43% p-y+ Took drug 77% p-y+ 4% study withdrawal	Open label Random-ization by sealed envelopes <u>Quality</u>: Fair
UKPDS-39, 1998 [188]	8.4 56	Captopril 400 Atenolol 358	144/83 143/81	20.2 16.9 *P* = 0.35	6.8 6.1 *P* = 0.74	<u>DM related death:</u> 15.2 12.0 *P* = 0.28	No difference vision, ESRD	<u>D/C study drug:</u> 22% 35% <u>Took study med:</u> Captopil 80% Atenolol 74% p-y+	Open Label <u>Quality</u>: Fair
CAPPP, 1999[189]; 2001[190]	6.1 55-56	Captopril 309 Conventional 263	155/89 153/88	3.9% 10.3% *P* = 0.002	7.4% 7.2% *P* = 0.96	<u>All cause:</u> 6.5% 12.9% *P* = 0.034	NR	One patient lost to follow-up; compliance with meds not given	Open Label <u>Quality</u>: Fair

Appendix B Evidence Table 4. Studies of Antihypertensive, ACE Inhibitors and ARB Medications (continued)

Study Population	Study Years Age	Groups N	BP Control	MI	Stroke	CVD Events Mortality	Non-CVD Outcomes	Adherence Withdrawal	Blinding Comments Quality
Brown et al., 2000 [191] INSIGHT	4 65	Nifedipine 649 Co-amilozide 653	138/82 138/82	NR	NR	CVD events: 8.3% 8.4%	NR	D/C study drug: 33.1% 39.9% 2.4% withdrew from study	Double-blind Randomi-zation Imbalance in DM-2 Quality: Fair
Estacio et al., 2000[192] ABCD	5 57	Moderate 233 Intensive 237	138/86 132/78	No difference	No difference	All-cause mortality: 10.7% 5.5% *P* = 0.037	No difference vision, ESRD, neuropathy	Participants on study drug ~70% of time.	Open label Quality: Fair
Hansson et al., 2000 [193] NORDIL	4.5 60-61	Diltiazem 351 Diuretics and/or Beta blockers 376	152/88 149/87	11.2* 11.1 *P* = 0.99	13.3* 12.3 *P* = 0.97	CVD events: 29.8* 27.7 *P* = 0.98	NR	On drug at end: 77% 93% <1% withdrawal from study	Open Label Quality: Fair

Appendix B Evidence Table 4. Studies of Antihypertensive, ACE Inhibitors and ARB Medications (continued)

Study Population	Study Years; Age	Groups N	BP Control	MI	Stroke	CVD Events Mortality	Non-CVD Outcomes	Adherence Withdrawal	Blinding Comments Quality
Lindholm Hansson et al., 2000 [194] STOP-2	5.3 75-76	ACEI 235	161/80	15.3*	31.6*	All cause: 49.0*		On drug at end: ACEI : 61.3%	Open Label
		CA 231	162/79	29.6 *P* = 0.025	26.9	43.9	NR	CA: 66.2% D/ß: 62.3%	For all participants, CHF and MI lower for ACE than CA group
		Conventional 253 (D/ß)	161/81	22.2	34.7 *P* = 0.36	55.5 *P* = 0.20		Study Withdrawal:0%	Quality: Fair
Brenner et al., 2001[84] RENAAL	3.4 60	Losarton 751	140/74	6.7%	NR	All-cause mortality: 6.8*	ESRD: 6.8*	Discontinued Treatment: 46.5%	Double-blind
		Placebo 762	142/74 *P* = 0.59	8.9% RRR: 28% *P* = 0.08		6.6* NS	9.1* RRR: 28% *P* = 0.002	53.5%	Randomized Quality: Good

Appendix B Evidence Table 4. Studies of Antihypertensive, ACE Inhibitors and ARB Medications (continued)

Study Population	Study Years; Age	Groups N	BP Control	MI	Stroke	CVD Events Mortality	Non-CVD Outcomes	Adherence Withdrawal	Blinding Comments Quality
Lewis et al, 2001 [195]	2.6 58-59	Irbesartan 579 Amlodipine 567 Placebo 569	140/47 141/77 144/80	NR	NR	CV outcome∓: 23.8 22.6 25.3 (NS)	Renal outcome†: 32.6% 41.1% 39.0% *P* = 0.006 *P* = 0.02	<1% study withdrawal	Double-blind Randomized by central office Quality: Good
Dahlof et al., 2002[116] LIFE	4 66.9	Losartan 4,605 Atenolol 4,588	144/81 145/81	9.2* 8.7* NS	10.8* 14.5* *P* = 0.001	All-cause mortality: 17.3* 19.6* *P* = 0.128	Diabetes: 13.0* 17.4* *P* = 0.001	Dropout: 105 pts 92 pts	Double-blind Randomized Quality: Good
Lindholm et al., 2002[117] LIFE (diabetics only)	4 67.4	Losartan 586 Atenolol 609	146/79 148/79	15.2* 18.7* *P* = 0.373	19.0* 24.5* *P* = 0.0204	All-cause mortality: 22.5* 37.2* *P* = 0.002	Renal Outcome†: No difference	Dropout: 32 pts 36 pts	Double-blind Randomized Quality: Good

* indicates events per 1,000 person – year; ∓, MI, stroke, cardiovascular death, amputation, congestive heart failure; †, doubling of creatinine, end-stage renal disease, any death

Evidence Table 5. Studies of Foot Care

Source Author, Year	Study Population: Selection & Description	Interventions/ Co-Interventions	Outcomes
Malone et al., 1989[102]	US Clinic-based Randomization: Randomized: 227 Did not fit criteria: 24 Included: 203 Incidence of prior distal vascular reconstruction higher in control group (NS) Incidence of foot callous was significantly higher intervention group $P \leq 0.05$ Inclusion: NIDDM patients with uninfected foot ulcers or prior amputation in VA hospital Exclusion: Patients requiring wound debridement, formal incision and drainage of foot infections, amputation, or vascular reconstruction until after definitive surgical tx	Intervention: 1-hour education class including a simple set of patient instructions for the care of the diabetic foot	Success defined as the continued absence of foot infections, ulceration, or foot or leg amputation

Evidence Table 5. Studies of Foot Care (continued)

Results	Quality Considerations And Comments
Results of diabetic education program Education / No education Success 90% / 72% Failure: Infection 1% / 1% Ulcer 5% / 15% Amputation 4% / 12%	Statistical analysis: Student's t-test Attrition: 21 patients died (13 in intervention, 8 in control) Quality: Fair

Evidence Table 5. Studies of Foot Care (continued)

Source/ Time Frame	Study Population: Selection & Description	Interventions/ Co-Interventions	Outcomes
Litzelman et al., 1993[103]	US Clinic-based Eligible: 728 Agreed to participate: 484 Assessed: 395 Completed: 352 Randomization: Randomly assigned 2 primary care teams to intervention, 2 to control. Intervention group had higher Hb A1C values than controls No differences found on other characteristics Inclusion: NIDDM, seen ≥ 2 times in preceding year by same provider; age >40 yrs; dx of diabetes >30 yrs; presence of disease requiring medication for control of hyperglycemia, intention to obtain care at practice for next 2 years, and body weight either ideal or heavier than usual Exclusion: Pregnancy; major psychiatric illness, including dementia; terminal illness likely to cause death in 1 year; renal failure; previous bilateral amputations above/below the knee; or an inability to provide self-care	Patient: Education session covering appropriate foot-care behaviors and footwear Behavioral contracts Phone and postcard reminders Health care system: Colorful folders with foot decals to identify intervention patients Health care providers: Patient-specific risk factors Patient-specific practice guidelines Have patients remove footwear for foot exams	Musculoskeletal and dermatologic abnormalities assessed using standard definitions of findings such as callus, hammer toe, and charcot foot Foot lesions defined as any wound, with or without functional interruption of the protective cutaneous barrier, ranging from a superficial scratch to an ulcer involving epidermis Serious foot lesion defined in standard way using Seattle wound classification system, severity grade of ≥ 1.3 Pressure and temperature sensations measured using 5.07-log-force Semmes-Weinstein monofilament and thermal sensitivity testing apparatus, according to standard techniques Thermal sensitivity considered abnormal if value >2 standard deviations from the mean value for healthy persons without diabetes

Evidence Table 5. Studies of Foot Care (continued)

Results

Effect of interventions on patient outcomes:

	OR (95% CI)	*P*-value
Serious foot lesions	0.41 (0.16-1.00)	0.05
All foot lesions	0.65 (0.36-1.17)	0.15
Interdigit maceration	0.63 (0.34-1.15)	0.13

Effect of intervention on self-foot-care behaviors:

	OR*(95% CI)	*P*-value
Inspect feet	0.23 (0.12-0.42)	<0.01
Inspect shoes	0.64 (0.40-1.00)	0.05
Lubricate feet	0.73 (0.44-1.22)	>0.20
Dry between toes	0.27 (0.19-0.75)	0.01

* OR < 1.0 means increased likelihood of behavior in intervention grp

Effect of intervention on physician documentation:

	Intervention (N=185)	Control (N=198)	*P*-value
Ulcers	23.8%	11.1%	<0.01
Pulse exam done	9.2%	3.0%	0.01
Dry/cracked skin	8.7%	2.0%	0.01

Quality Considerations and Comments

Statistical analysis:
Variables adjusted for baseline measurements
Standard analysis of covariance and logistic regression

Attrition:
43 (11%) did not complete study for following reasons: death (11), change of residence (15), illness (6), transportation problems (3), and misc reasons (8)

Quality:
Good

Limitations:
Neither the sample size nor the length of f/u was adequate to show if interventions reduced incidence of lower extremity amputations

Appendix B Evidence Table 6. Studies of Lipid Control

Source Author, Year	Study Population: Description	Study Population: Size	Study Population: Inclusion, Exclusion	Intervention	Outcomes (Primary, Secondary)	Results	Comments Quality
Elkeles RS et al., 1998[125] (SENDCAP)	Mean age: 50-51 years 67-75% male BMI: 28-29	164 from diabetes clinics at 5 British hospitals	Inclusion: Type 2 diabetes Ages: 35-65 No history of CVD At least one: Total cholesterol ≥ 200 Triglyceride ≥ 160 HDL ≤ 40	RCT 81 bezafibrate (400 mg/day) vs. 83 placebo Followup: 3 years	Primary: Ultrasonography of arterial disease Secondary: Documented MI & ECG changes indicating ischemia	No difference between groups in ultrasound arterial disease Definite CHD events bezafibrate: 7% placebo: 23% *P* = 0.01	Secondary endpoint Quality: Fair
LIPID Study Group, 1998[121]	Volunteers at 87 Centers Median age: 62 years 83% male	4,512 pravastatin 4,502 placebo	Inclusion: Past-MI or unstable angina Total cholesterol: 155-271 mg/dl Exclusion CHF or prior surgery	RCT pravastatin (40 mg/day) vs. placebo	Mortality from coronary heart disease Followup: 6.1 years (mean)	Death from coronary disease (%) pravastatin: 6.4% placebo: 8.3% RRR: 24% (12-35%) Overall mortality pravastatin: 11.0% placebo: 14.1% RRR: 22% (13-31%)	Quality: Good
Rubins HB et al., 1999 [122]	Volunteers at 20 VA medical centers Mean age: 64-65 years 100% male	1,264 gemfibrozil 1,267 placebo	Inclusion: Documented CHD Age: < 74 HDL: ≤ 40 LDL: ≤ 140 Triglyceride: ≤ 300	RCT gemfibrozil (1,200 mg/day) vs. placebo	Incidence of nonfatal MI and death from coronary heart disease Followup: 5.1 years (median)	CHD Event gemfibrozil: 17.3% placebo: 21.7% RRR: 22% (7-35%)	Quality: Good

Appendix B Evidence Table 6. Studies of Lipid Control (continued)

Source Author, Year	Study Population			Intervention	Outcomes (Primary, Secondary)	Results	Comments Quality
	Description	Size	Inclusion, Exclusion				
Sacks FM, 2002[123]	Secondary analysis of two secondary prevention studies (CARE & LIPID)	2,607 with LDL < 125 mg/ld	Inclusion: LDL < 125 at start Previous MI	RCT pravastatin (40 mg/day) vs. placebo Followup: 5-6 years	Aggregate CHD death + nonfatal MI + CABG/PTCA (coronary revascularization)	No difference in CHD events for any group (by age, other risk factors) except diabetes Diabetes pravastatin: 22% placebo: 34% RR=0.56 (0.37-0.83) No Diabetes pravastatin: 22% placebo: 21% RR=1.06 (0.89-1.27)	Quality: Good

Appendix B Evidence Table 7. Studies of IFG/IGT Screening and Treatment

Source: Author, Year	Study Population			Intervention
	Description	Size	Inclusion, Exclusion	
Pan X et al. 1997[141] Da Qing Impaired Glucose Tolerance and Diabetes Study	Mean Age: No differences in mean age (44.2 – 46.5 years) Gender: No difference Mean BMI: (25.3 – 26.3) Country: China Mean FPG (mmol/L): 5.52 (0.82) control 5.56 (0.81) diet modification 5.56 (0.83) exercise modification 5.67 (0.80) diet and exercise Mean follow-up: 6 years Note: Characteristics based on subjects completing study; data from those lost to follow-up not reported	Design: Prospective non blinded randomized clinical trial Randomized: 577 population-based IGT subjects identified from broad screening of city population of Da Qing, China Randomized to 4 groups 130 diet modification 141 exercise modification 126 diet and exercise modification 133 control	Fasting Glucose: WHO criteria based on sequential screening by FPG, OGTT tests Inclusion: Meeting WHO IFG criteria by FPG, OGTT testing Exclusion: None reported other than subjects with current NIDDM	Diet modification: Diet limiting caloric intake for subjects with BMI ≥25; supplemented with dietary counseling Exercise modification: Increased exercise recommended, supplemented with counseling Diet and exercise modification: Combination of above Control: General information regarding DM and IFG, diet and exercise modification

Evidence Table 7. Studies of IFG/IGT Screening and Treatment (continued)

Source: Author, Year	Outcomes	Results	Comments
Pan X et al. 1997[141] Da Qing Impaired Glucose Tolerance and Diabetes Study	Primary endpoints: Incidence of NIDDM Fasting hyperglycemia (FPG ≥7.8 mmol/L)	% Incidence of NIDDM: 67.7 control, 43.8 diet, 41.1 exercise, 46.0 diet and exercise modification (p=0.04) RRR 0.35 diet, 0.39 exercise, 0.32 diet and exercise modification ARR .239 diet, .266 exercise, .217 diet and exercise modification NNT (6 years) 5 diet, 4 exercise, 5 diet and exercise modification	Randomization based on study clinic, not patient; unable to evaluate effectiveness of randomization as baseline characteristics only reported for those completing study Not intent to treat analysis; exclusion of those who did not complete study Non-blinded assessment

Evidence Table 7. Studies of IFG/IGT Screening and Treatment (continued)

Source: Author, Year	Study Population			Intervention
	Description	Size	Inclusion, Exclusion	
Tuomilehto et al., 2001[143] Diabetes Prevention Trial	Mean Age: 55 Gender: 63%F Mean BMI: 31.3 Int. Grp: 31.3 (±4.6) Control: 31.0 (±4.5) Mean FPG (mmol/L): Int. Grp: 190 (±14) Control: 110 (±13) Time Frame: Up to 6 years Mean Follow-up: 3.2 years	Randomized: 522 middle-aged, overweight subjects with IGT Randomized to 2 groups: Intervention: N = 265 Control: N = 257	Design: Randomization by list, stratified by center, sex, mean PG Inclusion: BMI > 25, 40-60 yrs of age, and diagnosis of IGT by WHO criteria Exclusion: Diagnosis of diabetes, chronic disease with < 6 yr survival, psychological or physical disabilities	Intervention Grp: Individualized counseling on goals: Decrease weight ≥ 5% Fat Intake < 30% of Total Energy Consumed Sat Fat < 10% of Total Energy Consumed Fiber ≥ 15g/1000 kcal Exercise ≥ 30 min/day Control Grp: General oral and written materials about diet and exercise

Evidence Table 7. Studies of IFG/IGT Screening and Treatment (continued)

Source: Author, Year	Outcomes	Results	Comments
Tuomilehto et al., 2001[143] Diabetes Prevention Trial	Primary Endpoints: Incidence of DM	% Incidence of DM: Int. Grp: Per 1000 Person Years: 32; Cumulative Incidence After 4 Years: 11% Control Grp: Per 1000 Person Years: 78; Cumulative Incidence After 4 Years: 23% Persons who developed DM: Int. Grp: Number of Patients: 27; Average Per Year: 3% Control Grp: Number of Patients: 59; Average Per Year: 6% 13 pts of the Intervention Grp achieved no goals, of which 38% were later diagnosed with DM 48 pts of the Control Grp achieved no goals, of which 31% were later diagnosed with DM Risk of diabetes reduced by 58% ($P < 0.001$) in the Int Grp and directly associated with changes in lifestyle.	Intention to Treat Analysis Low drop out rate Quality: Good

Evidence Table 7. Studies of IFG/IGT Screening and Treatment (continued)

Source: Author, Year	Study Population			Intervention
	Description	Size	Inclusion, Exclusion	
Diabetes Prevention Program Research Group 2002[142]	Mean Age: 50.6 yrs Gender: 68%F Mean BMI: 34.0 Mean FPG: 106.5 mmol/L Mean Follow-up: 2.8 yrs	Randomized: 3,234 pts at high risk for DM 27 centers Groups: metformin - 1,082 placebo - 1,073 Lifestyle Modification Program - 1,079	Design: Randomization Inclusion: High risk for DM ≥ 25 yrs; BMI ≥24, FPG according to 1997 ADA criteria Exclusion: Taking medications known to alter glucose tolerance Serious illnesses to reduce life expectancy or ability to participate in trial	metformin: 850 mg 2xday Control: placebo only Lifestyle Modification Program Goals: ≥ 7% weight loss ≥ 150 minutes of physical activity per week

Evidence Table 7. Studies of IFG/IGT Screening and Treatment (continued)

Source: Author, Year	Outcomes	Results	Comments
Diabetes Prevention Program Research Group 2002[142]	Diagnosis of DM	Incidence Rate of DM: 11.0* Control Grp 7.8* metformin Grp 4.8* Lifestyle Grp Reduction of DM Incidence: 58% Lifestyle Grp (95% CI, 48-66) 31% metformin (95% CI, 17-43) To prevent one case of DM over 3 yrs, 6.9 persons would have lifestyle modification and 13.9 would receive metformin	Double-blinded Intention to treat analysis Quality: Good

Evidence Table 8. Studies of Harms of Screening or Treatment

Source Author, Year	Study Population	Measurements	Results	Comments Quality
UKPDS Group (UKPDS-33), 1998[30]	N: 3,867 (with newly diagnosed diabetes) Age: 25-65 Design: RCT (10 years followup) Intensive vs. conventional glucose control	Hb A1c over course of study Hypoglycemic episodes, all and major (involving medical care)	Median Hb A1c over study: Intensive: 70% Conventional: 79% Major hypoglycemia (% with one or more episodes/year) - insulin treatment: 2.3% - oral hypoglycemic drug: 0.4-0.6% - diet: 0.1%	Quality: Good
Testa, M.A, et al. 1998[163]	Description: 594 with diabetes age 30-85 RCT randomized to active glycemic treatment or placeby Gender: 54% (320) M Age: Mean= 58 yrs Range=30-85 yrs Country: US	Quality of life, days worked , health related days missed, restricted activity days, and health care use were assessed at screening, randomization, 4,8,and 12 wks	Treatment differences were more favorable for the active therapy arm vs placebo (symptom distress (+0.59, p<0.001), general perceived health (+0.36, *P* = 0.004), cognitive functioning (+0.34, *P* = 0.005), and overall visual analog score ratings (+0.24, p=0.04) Hypoglycemic symptoms were not significant between groups By week 15, absenteeism (missing ≥ ½ day/week) rose 8.1% (2.4 %-10.5%) for the placebo group and decreased 0.8% (5.6%-4.8%) for the active therapy group	Loss to f/u: 14.9% (30) in placebo group 9.4% (37) in glipizide GITS group Comments: Shows relationship between glycemic control and QOL Quality: Good

Evidence Table 8. Studies of Harms of Screening or Treatment

Source Author, Year	Study Population	Measurements	Results	Comments Quality
UKPDS 37, 1997[196]	N: 3,104 with newly diagnosed diabetes Ages: 25-65 RCT, randomized to intensive glycemic control and conventional Description: 2,431 (64% of sample) evaluated by specific question-naire 154 controls for specific question-naire 3,104 (85% of sample) evaluated by generic QOL measure 374 (82% of sample) followed longitudinally with specific question-naire with 184 (49%) followed to 6 yrs Gender: 59% (3,290) M Country: Great Britain	Questionnaires measuring cognitive mistakes, mood disruptions, symptoms and quality of life	Comparison with Control Subjects (specific questionnaire) QOL are Control Glucose (Pval) Symptoms 13 17 (0.0022) Cog mistakes 34.5 31 (<0.05) Vigor 17 16 (<0.05) Comparison of therapeutic policies on QOL: No significant differences in QOL between conventional and intensive blood glucose policies or between less tight and tight BP control policies	Loss to f/u: 672 (166 were untraceable or had emigrated) Comments: 2% (109/5426) had macro-vascular complications 1% (79/5456) had micro-vascular complications Design: 2 cross-sectional studies of patients enrolled in randomized controlled trials of 1-intensive vs. conventional glucose control and 2-tight vs less tight blood pressure control Quality: Good

Appendix B. Evidence Tables

Evidence Table 9. Studies of Cost, Cost-Effectiveness, or Modeling

Source: Author, Year	Study Methods	Study Population: Description	Time Frame	Outcomes Assumptions
CDC Diabetes Cost-Effectiveness Study Group, 1998[167]	Analysis: Cost-effectiveness of 1-time opportunistic screening for Type-2 DM Model: Monte Carlo simulation Inclusion: Persons age 25 and older from US general population Perspective: Single-payer health care system Country: US	Grp1: Hypothetical population without clinically diagnosed diabetes assigned to opportunistic screening or current clinical practice Grp2: 10,000 diabetics followed from onset of diabetes until death	Cohort followed from onset of diabetes until death	Outcome: Cost per additional life-year gained and cost per QALY gained Assumptions: Model parameters based on population surveys, epidemiological studies, clinical trials and other clinical studies. 1995 costs and benefits discounted at 3%
Brown Pedula et al., 1999[168]	Analysis: Cost analysis of complications in Type-2 DM Model: Ordinary Lease Squares Inclusion: People with diabetes from large grp-model HMO with clinical data Perspective: Health care system Country: US	11,768 members of HMO with Type-2 DM F: 49% >70 yrs: 32% ESRD: 11% CVD: 29%	9 yrs of clinical data	Outcome: Incremental cost of cardio-vascular and renal disease Assumptions: Patients assumed to have Type-2 DM if in registry after age 45 Costs in 1993 dollars

Evidence Table 9. Studies of Cost, Cost-Effectiveness, or Modeling (continued)

Results	Conclusions	Comments Quality
Screening all adults > 25 yrs Estimated Incremental Cost of Screening: $236,449/LY and $56,649/QALY gained Lifetime Reduction in Cum Incidence: ESRD 26% Blindness 35% LEA 22% Cost of Tx increased by $3,388 with 0.02 gain in life-yrs (1 wk) Screening all adults 25-34 yrs Estimated Incremental Cost of Screening: $35,768/LY and $13,376/QALY gained Lifetime Reduction in Cum. Incidence: ESRD 3.3% Blindness 7.5% LEA 2.9% Cost of Tx decreased by $1,275 with 0.13 gain in life-yrs (7 wks) Screening all African Americans 25-34 yrs Estimated Incremental Cost of Screening: $2,219/LY and $822/QALY gained Lifetime Reduction in Cum Incidence: ESRD 4.6% Blindness 8.8% LEA 4.2% Cost of Tx decreased by $5,539 with 0.15 gain in life-yrs	Screening is more cost-effective on younger people and among African Americans. Benefits of early detection and treatment include postponement of complications	Comments: Direct nonmedical or indirect costs not considered. Quality: Good
Independent Contributions to Health Care Costs of CVD and Renal Complications in Type-2 DM: No CVD or Renal Disease: $2,033 Age (per 10 y): -$67 F: $1,105 CVD Preventive Tx: $1,087 CVD Postevent Tx: $7,352 Abnormal Renal Complication: $1,337 Advanced Renal Complication: $3,979 ESRD: $15,675	On the population level, greatest cost savings would be achieved by preventing CVD On the individual level, greatest savings achieved by preventing ESRD	Quality: Good

Evidence Table 9. Studies of Cost, Cost-Effectiveness, or Modeling (continued)

Source: Author, Year	Study Methods	Study Population: Description	Time Frame	Outcome Measure/ Assumptions
Brown Nichols et al., 1999[166]	Analysis: Cost analysis of incremental costs after Type-2 DM diagnosis Case-control method; cumulative incidence cohort Inclusion: People with new diagnosis of diabetes from large group model HMO with clinical data Perspective: Health care system Country: USA	8,685 members of HMO with new diagnosis of Type-2 DM F: 47% Year 1 50% Year 2 Mean age: 59.6 ≥ 65 years: 38.4%	8 yrs of clinical data	Outcome: Incremental cost of treatment Assumptions: Patients assumed to have Type-2 DM if in registry after age 45 Costs in 1993 dollars

Diabetes-associated incremental costs: Average $2,257 per person per year (Hospitalizations for non-diabetes causes accounted for increased costs in years 1, 7 and 8) Acute Inpatient Care: Hospital Admissions accounted for $8,236 per person, or 46% of 8 yr total (largest share of incremental costs) Hospitalizations account for most of the drop after Year 1, some of steady growth thereafter, and almost all annual fluctuation Per Person Over 8 Yrs / Per Person Per Year / % of Total Costs Cardiac $1,422 / $178 / 17 Cerebrovascular $ 488 / $ 61 / 6 Outpatient Care: 24-29% of total incremental costs (26% for all 8 years) Ave $292 per year for primary care Ave $303 per year for specialty care Over 8 yr: $2,336 for primary care, $2,424 for specialty Incremental costs of diabetes after year 1: About $100 per year (Year 1 costs spike due to non-diabetic causes) Diabetes complication hospitalizations: $136 per person per year $1,087 per person over 8 years Outpatient Drugs and Supplies: After year 1 – rapid growth in cost of antihyperglycemic drugs and supplies account for 5.9% of total costs Drug costs varied from 20% in Year 1 to 33% in Year 2 Outpatient and Pharmacy costs average $633 per year or $5,060 per person over 8 yr total Annual Incremental Costs: Year 1 - $2,392 Year 2 - $1,707 Year 8 - $2,817 Other: No growth found during first 8 years in hospital and pharmacy due to CVD and renal disease	Diagnosis of diabetes more than doubled the costs incurred by age, sex, and eligibility – matched people without diabetes Diabetes complications do not increase incremental costs as early as is commonly believed when growth for costs due to aging is controlled for Over 8 years, diabetes more than doubled the inpatient cost of cardiac disease, tripled the inpatient cost of cerebrovascular disease, and quadrupled the cost of admission for other CVD problems	Quality: Good

Evidence Table 9. Studies of Cost, Cost-Effectiveness, or Modeling (continued)

Source: Author, Year	Study Methods	Study Population: Description	Time Frame	Outcomes Assumptions
Vijan et al., 1997[197]	Analysis: Estimate benefits of intensive glycemic control in patients with Type-2 DM Model: Markov decision model Inclusion: HMO patients with Dx of diabetes Perspective: Clinical risks and benefits Country: US	NR	Cohort followed from onset of diabetes until death	Outcome: Risks for developing blindness and ESRD, NNT Assumptions Model based on DCCT Patients assumed to have no microvascular complications at Dx. Retinop. and micro-albuminuria tied to glycemic control
UKPDS 40 1998[198]	Analysis: Cost-effectiveness analysis to estimate economic efficiency of tight BP control Model: Not reported Inclusion: Hypertensive patients with diabetes from 20 hospital-based clinics in England, Scotland, and N. Ireland Perspective: Healthcare purchaser Country: UK	1,148 patients Age: 56.4 yrs F: 46% Grp 1: tight BP control Grp 2: less tight BP control	Trial cohorts run through model until death	Outcome: CER based on 1) use of health care resources 2) trial time free from diabetes Assumptions: Model based on UKPDS trial Costs in 1997 pounds sterling

Evidence Table 9. Studies of Cost, Cost-Effectiveness, or Modeling (continued)

Results	Conclusions	Comments/ Quality Issues
Lifetime Risks for Blindness and ESRD (diabetes onset b/f age 50) Blindness / ESRD Hb A1c 9%: 2.6% / 3.5% Hb A1c 7%: 0.3% / 2.0% Lifetime Risk for Blindness and ESRD (diabetes onset at age 65) Blindness / ESRD Hb A1c 9%: 0.5% / 0.6% Hb A1c 7%: <0.1% / 0.3% NNT: Offering intervention of intensive glycemic control to the 29.3% of patients with HbA1c levels of 9% or greater, one case of blindness would be prevented for every 181 persons treated for life	Targeting patients on the basis of age at diabetes onset can improve the efficiency of the intervention of intensive glycemic control	Comments: Model based on extrapolation from experience of Type-1 DM Quality: Good
Treatment costs over trial duration: Tight Control £4,245 Less Tight Control £3,505 Complication costs (hospitalization): Tight Control £2,930 Less Tight Control £3,603 Total costs (present value discounted at 6%): Tight Control £7,081 Less Tight Control £7,156 Time free from diabetes-related endpoints: Undiscounted / 6% Tight Control 8.16 yrs / 4.85 yrs Less Tight Control 7.61 yrs / 4.63 yrs Incremental cost per life-Yr gained: Cost and effects discounted at 6% *£720* Only costs discounted at 6% £291	Tight control of BP reduced cost of complications, and increased time w/o complications	Limitations: Costs based on trial protocol driven costs and not costs of standard practice Comments: Only direct health service costs analyzed. Quality: Good

Evidence Tables Glossary

Abbreviation	Definition
ACEI	Ace Inhibitors
ADA	American Diabetes Association
ARR	Absolute Relative Risk
BMI	Body Mass Index
CA	Calcium Channel Blockers
CABG	Coronary Artery Bypass Graft
CBG	Capillary Blood Glucose
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
Cog	Cognitive
CVD	Cardiovascular Disease
DB	Diuretics and Beta Blockers
D/C	Discontinued
ECG	Electrocardiogram
ESRD	End State Renal Disease
FPG	Fasting Plasma Glucose
Grp	Group
Hb A1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
Int	Intervention
LEA	Lower Extremity Amputation
LDL	Low-Density Lipoprotein

MI	Myocardial Infarction
New-DM	Newly Diagnosed Diabetes
NGT	Normal Glucose Tolerance
NHANES	National Health and Nutrition Examination Survey
NNT	Number Needed to Treat
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
p-y	Person year
PG	Plasma Glucose
PTCA	Percutaneous Transluminal Coronary Angioplasty
QALY	Quality Adjusted Life Year
QOL	Quality of Life
RR	Relative Risk
RRR	Relative Risk Reduction
TX	Treatment
WHO	World Health Organization

Figure 1. The "Delta Question" in Screening for Type 2 Diabetes

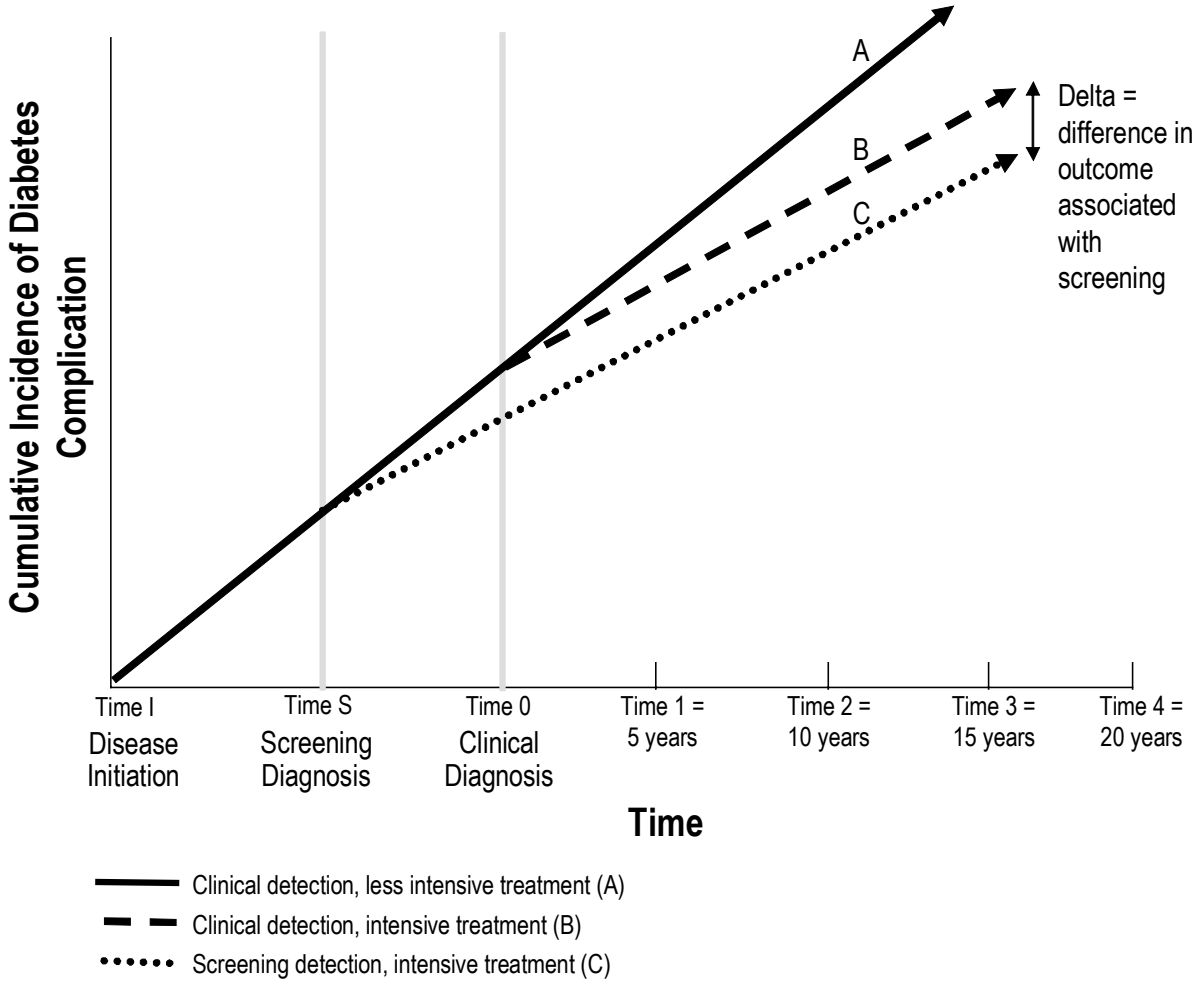

Figure 2. Screening for Type 2 Diabetes: Analytic Framework

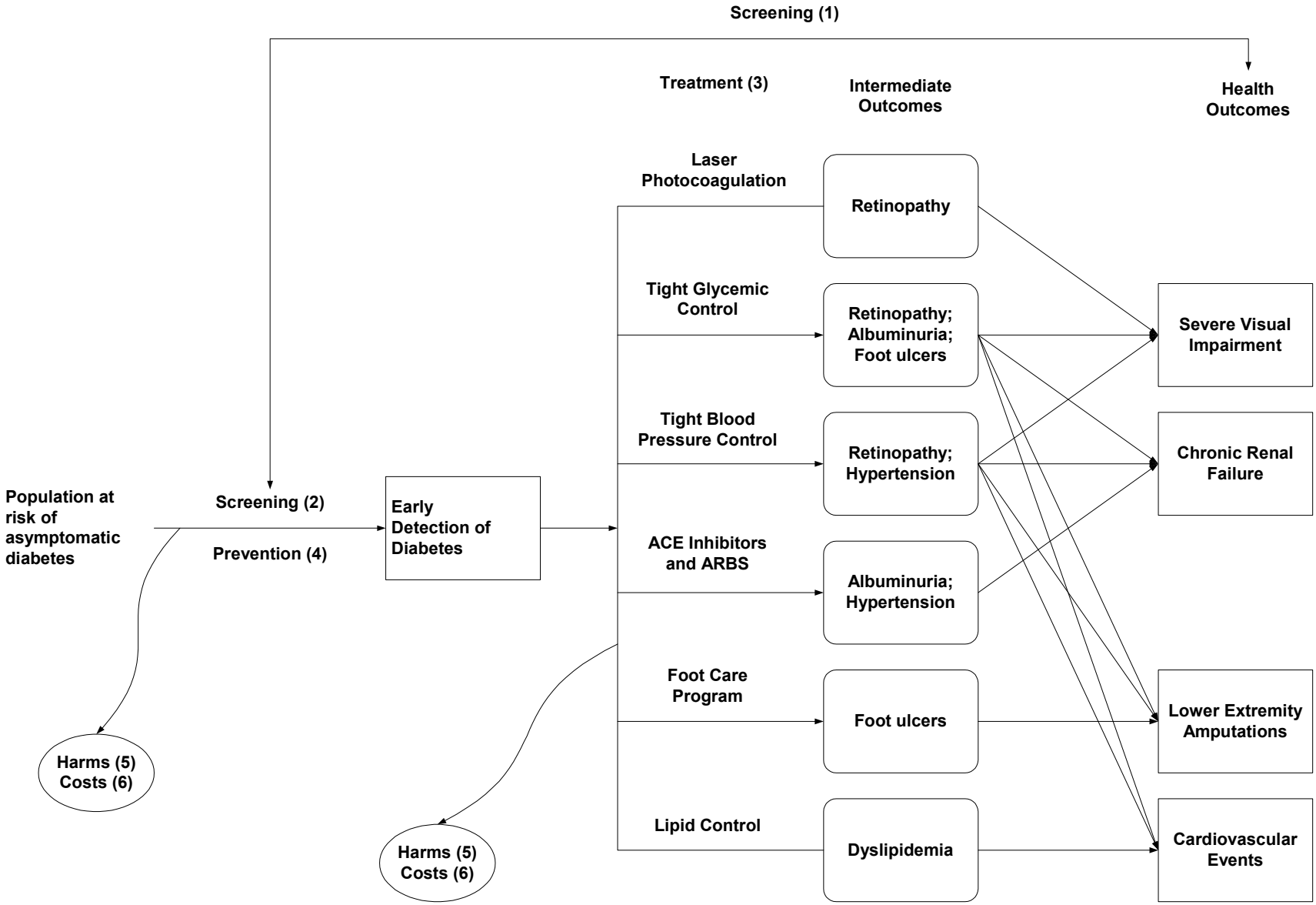

Table 1. Screening for Type 2 Diabetes: Key Questions

Key Question 1:	Is there direct evidence from a randomized controlled trial of screening that screening for diabetes improves health outcomes?
Key Question 2:	What is the yield of screening, in terms of the accuracy and reliability of screening tests and the prevalence of undiagnosed diabetes in the population?
Key Question 3:	What is the added efficacy of initiating the treatments below at screening detection rather than at clinical detection in improving health outcomes: - laser photocoagulation? - tight glycemic control? - tight blood pressure control? - ACE inhibitors and ARBs*? - foot care programs? - lipid control?
Key Question 4:	What is the efficacy of lifestyle intervention for people with impaired fasting glucose or impaired glucose tolerance in improving health outcomes?
Key Question 5:	What are the harms of screening or treatment?
Key Question 6:	What are the costs and cost-effectiveness of screening?

* indicates angiotensin-converting enzyme (ACE) inhibitors; ARBs, angiotensin receptor blockers (ARBs).

Table 2. Number Needed to Screen (NNS) for Diabetes to Prevent One Case of Blindness in One Eye by Tight Glycemic Control

Case 1: Screen 1,000 persons with BP>= 140/90
Assume:

a. 6% prevalence of undiagnosed diabetes
b. 5 years of additional treatment for diabetes
c. 1.5% 5-year risk of blindness in one eye with loose (no) glycemic control*
d. 29% relative risk reduction for blindness in one eye with tight glycemic control†
e. Screening produces 100% absolute increase in the percentage of diabetics with tight glycemic control (i.e., all newly detected diabetics achieve adequate control)

Number of diabetics detected by screening	60
Number of cases of blindness in one eye after 5 years, among the 60 newly detected diabetics	If 0% achieve tight control, 0.90 If 100% achieve tight control, 0.64
Difference: number of cases of blindness prevented**	0.26
Number needed to screen (NNS)‡ to prevent one case	3,900

Case 2: Same as Case 1, except that we vary the absolute increase in the percentage of diabetics with tight control produced by screening.

Screening increases the percentage of newly detected diabetics with tight glycemic control by:	Cases Prevented **	NNS ‡
10%	0.03	38,400
25%	0.07	15,400
50%	0.13	7,700
75%	0.20	5,200
90%	0.23	4,300

Case 3: Same as Case 2, except that we assume that screening produces only 2.5 years of additional treatment rather than 5 years, thus decreasing the number of cases of blindness prevented by 50%.

Screening increases the percentage of newly detected diabetics with tight glycemic control by:	Cases Prevented **	NNS ‡
10%	0.01	76,700
25%	0.03	30,700
50%	0.07	15,400
75%	0.10	10,300
90%	0.12	8,600

Case 4: Same as Case 3, except that we assume that the prevalence of undiagnosed diabetes is 3%, rather than 6%, thus decreasing the number of cases of blindness prevented by a further 50%.

Screening increases the percentage of newly detected diabetics with tight glycemic control by:	Cases Prevented **	NNS ‡
10%	0.01	153,300
25%	0.02	61,400
50%	0.04	30,700
75%	0.06	20,500
90%	0.07	17,000

* Loose glycemic control is equivalent to no treatment for hyperglycemia

† Based on assumption that reduction in the relative risk of blindness in one eye attributable to tight glycemic control is equal to the reduction in the rate of retinal photocoagulation in the UKPDS study [169].

** Cases prevented calculations rounded to nearest 0.01.

‡ All NNS calculations are rounded upward to nearest hundred.

Table 3. Number Needed to Screen (NNS) for Diabetes to Prevent One Cardiovascular (CVD) Event by Tight Blood Pressure Control

Case 1: Screen 1,000 persons with blood pressure >= 140/90

Assume:

a. 6% prevalence of undiagnosed diabetes among those with elevated blood pressure levels
b. 5 years of additional treatment for elevated blood pressure
c. 7.5% 5-year risk of CVD event with loose blood pressure control*
d. 50% relative risk reduction in CVD events with tight blood pressure control†
e. Screening produces 100% absolute increase in the percentage of diabetic hypertensives with tight control of blood pressure

Number of diabetics detected by screening	60
Number of CVD events after 5 years, among the 60 diabetic hypertensives detected	If 0% achieve tight control, 4.50 If 100% achieve tight control, 2.25
Difference: CVD events prevented**	2.25
Number needed to screen (NNS) to prevent one CVD event‡	500

Case 2: Same as Case 1, except that we vary the absolute increase in the percentage of diabetic hypertensives with tight blood pressure control produced by screening.

Screening increases the percentage of diabetic hypertensives with tight blood pressure control by:	CVD Events Prevented**	NNS‡
10%	0.23	4,500
25%	0.56	1,800
50%	1.13	900
75%	1.69	600
90%	2.03	500

Case 3: Same as Case 2, except that we assume screening produces only 2.5 years of additional blood pressure treatment, thus decreasing the number of CVD events prevented by 50%.

Screening increases the percentage of diabetic hypertensives wth tight blood pressure control by:	CVD Events Prevented**	NNS‡
10%	0.11	8,900
25%	0.28	3,600
50%	0.56	1,800
75%	0.84	1,200
90%	1.01	1,000

Case 4: Same as Case 3, except we assume prevalence of undiagnosed diabetes is 3%, rather than 6%, thus decreasing the number of CVD events prevented by a further 50%.

Screening increases the percentage of diabetic hypertensives with tight blood pressure control by:	CVD Events Prevented**	NNS‡
10%	0.06	17,800
25%	0.14	7,200
50%	0.28	3,600
75%	0.42	2,400
90%	0.51	2,000

* Loose blood pressure control is equivalent to a diastolic goal of 90mm Hg; tight blood pressure control is having a diastolic goal of 80mm Hg.

† Based on results for intensive treatment to lower pressure from the Hyptertension Optimal Treatment (HOT) trial. [170]

** All CVD events prevented calculations are rounded off to nearest 0.01.

‡ All NNS calculations are rounded upward to nearest hundred.