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Screening for Type 2 Diabetes Mellitus: Update of 2003 Systematic Evidence Review for the U. S. Preventive Services Task Force

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Structured Abstract

Background: Diabetes poses a tremendous and increasing clinical and public health burden for Americans; 19.3 million Americans over the age of 20 years are affected, one third of whom are undiagnosed.

Purpose: To examine the evidence of the potential benefits and harms of screening adults for type 2 diabetes mellitus (DM2) and prediabetes in primary care settings in the United States.

Data Sources: We searched Medline and the Cochrane Library for reviews and relevant studies published in English between March, 2001 and July, 2007.

Study Selection: Studies of any design which examined the effects of a DM2 screening program on long-term health outcomes were included. Randomized controlled trials (RCTs) examining the effects of treatments for DM2 in persons with disease duration ≤ 1 year and prediabetes treatment studies were also included, as were RCTs where treatment effects were compared between persons with diabetes and normoglycemia.

Data Extraction: Data were abstracted by one author and checked by a second. Key studies were reviewed and discussed by all authors.

Results: There were no RCTs examining the effectiveness of a DM2 screening program. A small, case-control study did not suggest a benefit from screening when microvascular complications were considered. No study directly compared treatment effects between screen-detected and clinically-detected diabetic persons, nor have studies to date reported treatment effects in a screen-detected cohort with diabetes. Modeling studies suggest that screening for DM2 may be relatively cost-effective when macrovascular benefits of optimal blood pressure control are taken into account.

There was no clear evidence that persons with DM2 detected by screening would respond differently to specific antihypertensive regimens compared to persons without diabetes, and persons with diabetes and no known cardiovascular disease benefit from aggressive lipid control to a similar extent as persons without diabetes, but with known cardiovascular disease. In two new studies, aspirin did not appear to reduce the risk of myocardial infarction in DM2, but may lower the risk of ischemic stroke in women. There were no new data examining glycemic control strategies in persons with newly-diagnosed DM2.

Intensive lifestyle and various pharmacotherapeutic interventions decrease the incidence of DM2 over follow-up periods up to 7 years. There were little data, however, on the prevention or delay of cardiovascular and other long-term health outcomes, including death. Limited data from observational studies suggest no serious adverse effects of receiving a diagnosis of DM2 from screening. Recent systematic reviews of the adverse effects of drugs used in the treatment of DM2 and prediabetes do not reveal significant new data on harms.

Limitations: Direct trial evidence of the benefits or harms of screening is lacking, therefore we relied solely on indirect evidence. Since the natural history of prediabetes and DM2 is not well elucidated, it remains unclear as to how applicable data from persons with DM2 ≤ 1 year is to screen-detected persons. Most of the treatment data are from subgroup analyses of large trials, which may be underpowered to address the comparisons of interest. The prediabetes studies had limited power and an insufficient length of follow-up to determine health outcomes in prediabetic persons.

Conclusions: There is no direct trial evidence of the effectiveness of screening for DM2 or prediabetes. Data from the prior US Preventive Services Task Force review lead to recommendations that persons with DM2 with hypertension or hyperlipidemia benefit from screening for DM2; we identified few additional, relevant studies. There is evidence that lifestyle and pharmacotherapy can delay the progression of DM2 among persons with prediabetes, but little direct evidence that identifying persons with prediabetes will lead to long-term health benefits, although longer-term follow-up of these trials has yet to be completed.

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I. INTRODUCTION

Scope and Purpose

The objective of this systematic review is to examine the evidence for the potential benefits and harms of screening adults over the age of 20 years for type 2 diabetes mellitus (DM2), and for impaired fasting glucose (IFG) and/or and impaired glucose tolerance (IGT) (prediabetes) in primary care settings in the United States (US). The evidence presented will be used by the US Preventive Services Task Force (USPSTF) to formulate clinical practice recommendations.

Definition of Diabetes

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] DM2, previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for 90% to 95% of all diagnosed cases of diabetes. DM2 encompasses individuals who have insulin resistance as well as defective insulin secretion such that insulin levels are insufficient to compensate for the insulin resistance (i.e., a relative, rather than absolute, insulin deficiency).[1]

There is an intermediate group of persons who do not fulfill the definition of DM2, but who do not have normoglycemia. These persons have IFG [fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l)] or IGT [2-h values in the 75-gm oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l)]. Persons with IFG and/or IGT are referred to as having prediabetes. (See Appendix A1 for diabetes definitions, and Appendix A2 for abbreviations referenced in this report.)

Prevalence and Burden of Disease

Diabetes poses a tremendous clinical and public health burden for Americans. Data from the National Health and Examination Survey (NHANES) indicated that 19.3 million Americans (9.3% of the total US population) 20 years of age and older had diabetes in 2002, one third of whom were undiagnosed.[2] An additional 26.0% had IFG. The prevalence of diagnosed diabetes rose from 5.1% in 1988–1994 to 6.5% in 1999–2002,[2] and is increasing most rapidly among individuals with a body mass index (BMI) of ≥ 35 kg/m.[2, 3] The prevalence of diabetes (diagnosed and undiagnosed) rises with age, reaching 21.6% for those aged 65 years of age or more. Other factors may play a role in the increasing diabetes prevalence, including reductions in physical activity, dietary changes, an increase in survival, or more frequent diagnosis.[3] African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or other Pacific Islanders are at particularly high risk for DM2.[4] The prevalence of diagnosed diabetes is twice as high in non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites.[2]

Diabetes was the sixth leading cause of death listed on US death certificates in 2000, and diabetes is likely to be underreported as a cause of death.[4] Overall, the risk for death among people with diabetes is about twice that of people without diabetes. Adults with diabetes have rates of stroke and death from heart disease that are about 2 to 4 times higher than adults without diabetes. Diabetes is the leading cause of new cases of blindness among adults aged 20-74 years and the leading cause of end-stage renal disease, accounting for 44% of new cases. More than 60% of nontraumatic lower-limb amputations occur among people with diabetes.[4]

The estimated total costs of diabetes in the US in 2002 were $132 billion, of which $92 billion were direct medical costs. Indirect costs such as those due to disability, work absenteeism and premature mortality are estimated at $40 billion.[4]

Etiology and Natural History of Diabetes

The specific etiologies of DM2 are not known; however, the disease is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Both genetic susceptibility and environmental factors likely contribute to the development of DM2. Insulin resistance and beta-cell dysfunction (i.e., the inability of the pancreas to secrete sufficient insulin in response to glucose levels) are both implicit in the pathogenesis of the disease.[5] The process of glycemic dysregulation typically begins long before symptoms develop. It is estimated that, on average, persons with clinically diagnosed diabetes will have lost up to 50% of their beta cell mass by the time of diagnosis.[6]

The natural history of diabetes and prediabetes may proceed through different pathways, with differing rates of progression from normoglycemia through IFG, IGT, to DM2.[7, 8] This progression occurs over many years; by 20 years of follow-up of a normoglycemic cohort, 71% had developed IGT and 39% IFG. Metabolic data also suggest that there are important differences between IFG and IGT, and there is some evidence that IGT may be a stronger predictor of cardiovascular complications than IFG.[9, 10] Persons with prediabetes have a 20 to 30% risk for development of DM2 over 5 to 10 years.[7, 11] Some persons with IGT can revert to normoglycemia.[12] It is unclear if the rate of decline in beta cell function is linear or the same for the progression of prediabetes to diabetes and for undiagnosed DM2 to clinical presentation.[13]

DM2 often goes undiagnosed for many years because the hyperglycemia develops gradually and may not produce symptoms.[3, 14] However, such patients are at increased risk of developing microvascular and macrovacular complications. The prevalence of advanced microvascular complications such as proliferative retinopathy is relatively low at clinical diagnosis and duration of diabetes and degree of hyperglycemia are associated with increasing risk of these complications.[15-18] The rate of progression to retinopathy, neuropathy, and microalbuminuria is likely accelerated in those with increased age at diagnosis.[19]

The epidemiology of macrovascular complications differs from that of microvascular complications: cardiovascular morbidity and mortality are substantially elevated well before diagnosis of diabetes and are also elevated in persons with prediabetes and newly-diagnosed

diabetes.[20-28] A substantial proportion of persons presenting with a new cardiovascular event have undiagnosed diabetes or prediabetes.[20, 29-33] Though there is good evidence linking chronic hyperglycemia to microvascular complications, the relationship between degree of hyperglycemia and macrovascular complications is less clear. Several recent observational studies and a meta-analysis do suggest a relationship between chronic hyperglycemia and cardiovascular disease and stroke, both in patients with and without known diabetes.[34-37]

Rationale for Screening and Screening Strategies

For screening to be effective in decreasing the complications and mortality from DM2, there must be: 1) a detectable preclinical period; 2) valid and reliable screening tests to detect the disease during that period; and 3) effective treatments for diabetes or related medical conditions during the preclinical phase that reduce morbidity and mortality compared to treatments starting at the time of clinical (symptomatic) diagnosis. Treatments may be different for persons with and without DM2, so that knowledge of diabetes would prompt a change in clinical management, for example, use of a different medication or a different treatment target.

Diabetes has a long preclinical phase, estimated at between 10 and 12 years based on the progression of microvascular complications.[38] There are currently valid and reliable tests for screening for DM2. The American Diabetes Association (ADA) recommends a FPG test, repeated in the absence of symptoms.[1] The specificity of a single FPG with a cut-point of 126 mg/dl is > 95% and the sensitivity about 50% (lower for older adults), when compared to a 2-hour OGTT.[39]

As Harris and colleagues described in the prior evidence review for the USPSTF,[40] screening is justified if it offers incremental benefits beyond the level of effectiveness of usual care at the time of clinical presentation (see Figure 1). If treatments are started at the time of screening diagnosis, do they reduce the incidence of complications (Line C) below that which would likely occur if treatment commenced with clinical presentation (Line B)? The vertical difference between lines B and C is the reduction in incidence of complications achieved by starting treatment with screening rather than later with clinical diagnosis and treatment. The harms and economic costs of screening and treatment must be small enough so that they do not outweigh the benefits of earlier treatment of screen-detected persons.

In addition to the necessity for a long preclinical phase, a valid screening test, and effective treatments for screened positive persons, a screening program must be feasible. Feasibility is determined by a number of factors: acceptability of the program to potential screenees; access to health services and appropriate treatment for persons who screen positive; cost-effectiveness; and the yield of cases. We will not address acceptability and access in this report, but will briefly address cost-effectiveness, as described in modeling studies.

Yield is the number of cases detected by a screening program. This includes positive predictive value (the probability that a person actually has the disease given that he or she screens positive) and negative predictive value. Predictive value depends on factors that determine the validity of the test as well as the prevalence of undiagnosed disease in screened populations. As the number

of risk factors for DM2 (and thus the prevalence of undiagnosed disease) increases, the yield of screening for DM2 will increase. Screening can be targeted (selective) when directed at individuals with a high prevalence of risk factors; opportunistic when screening persons at provider visits; or universal (mass) screening when an entire population is screened.[41]

Re-Screening Intervals

Subsidiary Question 1. What are the yields (accuracy and reliability) of different re-screening intervals among persons with an initial normal fasting glucose?

We identified only one study which directly examined re-screening intervals,[42] in addition to several modeling studies.[43-45] A fair-quality, longitudinal cohort study[42] followed annual fasting serum glucose levels in healthy, community-based volunteers over 65 years of age for up to 18 years (n = 299) (see Appendix Table B1). Of subjects without diabetes at baseline, 1.3% developed DM2 over the follow-up period. Fasting glucose decreased over time in most participants, and in 16% of subjects the rate of decrease was significant ($p<0.05$); in only 3% was the rate of increase significant. None of the subjects over the age of 75 years at baseline (n=68) developed diabetes or had a significantly positive slope. The authors concluded that it is not necessary to screen non-obese persons (excluding minorities) over 65 years of age who have a baseline fasting glucose of less than 100 mg/dl, and it is not necessary to screen persons over age 75 years every 3 years. This study involved a group of healthy and health-conscious Caucasian participants, and is not likely to be applicable to broader populations. In addition, half of the original cohort was lost to follow-up.

Several modeling studies have examined screening intervals. In a Markov model, Chen and colleagues[43] found that the number of quality-adjusted life-years (QALYs) gained was similar with screening intervals of 2 and 5 years, but the 5-year screening interval was more cost-effective (incremental cost per QALY $10,531 compared with $17,833) due to the higher costs of screening more frequently. A simulation of alternative DM2 screening intervals (1, 3, and 5 years) and random glucose cut-off levels (100, 130, and 160 mg/dl) for the US population aged 45 to 74 years[44] found that screening every 3 years with a random glucose cut-off of 130mg/dl provided optimal yield and minimized false-positive test results and screening costs.

For groups in whom DM2 screening is recommended, the frequency with which that screening should occur is unclear. Screening frequency is dependent on the rate of rise of blood glucose over time, and data are sparse on this progression and how it may vary across the age spectrum, between sexes, and among different races or ethnic groups. Screening interval could be contingent on the results of the first screen, as suggested by Waugh and colleagues.[13] The ADA recommends screening every 3 years if the test is normal[46] based on expert opinion and the rationale that false negative results will be repeated before substantial time has elapsed.

A1c Screening Test

Subsidiary Question 2. What is the yield (accuracy, reliability, and prevalence) of screening for type 2 diabetes with A1c?

The OGTT diabetes screening tool has been in use for many years and has served as a gold standard for diabetes diagnosis in a number of large epidemiological studies, but it is cumbersome to perform and is no longer recommended for routine clinical use by groups such as the ADA.[2] FPG is a commonly performed screening test, but the stipulation of fasting introduces possible barriers to use in clinical settings. Moreover, FPG may not reliably identify those with post-prandial hyperglycemia.[9, 47-49] Therefore, there has been significant interest in evaluating A1c as a potential screening tool,[50-65] (see Appendix Table B2) as A1c correlates with glucose intolerance as defined by OGTT results, does not require fasting, and is relatively easy to perform in the primary care setting. A1c levels predict microvascular complications in persons with DM2 and may also predict macrovascular complications in those with and without diabetes across a range of A1c values.[15-18, 36, 37, 66] In the past, the utility of A1c as a screening tool was limited in part by its relatively poor reproducibility and the lack of standardization across labs. More recently, there has been widespread adoption of standardized A1c measurements, as newer techniques for measurement are generally highly reproducible across a wide range of A1c values, though inter-individual biologic variability is present.[67-69]

A fair-quality systematic review in 1996 found that an A1c cutoff of 6.4% was 66% sensitive, 98% specific, and was associated with a positive predictive value of 63% in a population with a diabetes prevalence of 6%.[61] Increasing the cutoff to 7% increased the positive predictive value to 90%. The authors argued that an A1c cutoff of 7% was reasonable since it was associated with low false positive rates and because values higher than this would generally prompt consideration of pharmacologic treatment, while the clinical approach to lower values would focus mainly on lifestyle modification. Because this review is older, the included studies do suffer from the potential for variability from lack of standardization of A1c assay methodology across studies.

A recent good-quality systematic review examined studies through 2004 that compared the operating characteristics of A1c and FPG in detecting diabetes and prediabetes as defined by OGTT results according to World Health Organization (WHO) criteria.[51] The review found that FPG and A1c were similarly effective in detecting diabetes, but both had low sensitivity (about 50%) for detection of IGT. Though there were a variety of different cutpoints examined, many studies found that the optimum Diabetes Control and Complications Trial (DCCT) -aligned A1c cut-point was $\geq 6.1 - 6.2\%$, with corresponding sensitivities 43-81% and specificities 79-99%. We identified 9 studies published since, or excluded from, this review examining the utility of A1c as a screening test for DM2 with results also suggesting moderate sensitivity and high specificity of A1c values in a comparable borderline range.[50, 52, 54-56, 58, 63-65] A1c values in the high-normal range (5.6 – 6.0%) appear to predict a higher incidence of future diabetes,[54, 60] and values in this range seem to be the most cost-effective for diagnosing diabetes (though a lower cutpoint of 5.0% would be most efficient for diagnosing both prediabetes and diabetes).[70]

Several studies underscored the improved sensitivity of A1c in detecting abnormal glucose tolerance in high-risk ethnic groups.[50, 55, 64]

In summary, A1c is a convenient and potentially clinically meaningful screening test with sensitivity and specificities similar to, or better than, FPG at cutpoints in the high-normal/borderline range. Technical issues with the test may limit its current application as a screening test, though widespread standardization efforts are underway.

IFG, IGT, and Incidence of Diabetes

Subsidiary Question 3. Does beginning treatment for IFG or IGT early as a result of screening decrease the incidence of diabetes compared with initiating treatment after clinical diagnosis?

This question was systematically reviewed and incorporated into Key Question 3 in the Results Section of this report.

Recommendations of Other Groups

Many public and private groups internationally have made recommendations on screening for DM2 (Table 1). The ADA recommends that testing be considered in all adults at age 45 years and above, particularly those with BMI $\geq$ 25 kg/m^2; and if testing is normal, it should be repeated at 3-y intervals.[46] Testing should be also considered in younger adults or carried out more frequently among persons with risk factors for DM2. The ADA states that these recommendations are based on expert consensus or clinical experience.[1] The American Academy of Family Physicians follows the recommendations of the USPSTF.[71] The Australian Evidence-based Guideline recommends screening each year for people with IGT or IFG, and every 3 years for people with high risk and a negative screening test.[72] The United Kingdom Position Statement recommends targeted case finding.[73] The WHO does not recommend screening.[74]

Previous USPSTF Recommendations

In 2003 the USPSTF made two recommendations regarding screening for DM2:[75]

1. *The USPSTF concludes that the evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose. I recommendation.*

The USPSTF found good evidence that available screening tests can accurately detect type 2 diabetes during an early, asymptomatic phase. The USPSTF also found good evidence that intensive glycemic control in patients with clinically detected (not screening detected) diabetes can reduce the progression of microvascular disease. However, the benefits of tight glycemic control on microvascular clinical outcomes take years to become apparent. It has not been demonstrated that beginning diabetes control early as a result of screening provides an incremental benefit compared with initiating treatment after clinical diagnosis. Existing studies have not shown that tight glycemic control significantly reduces macrovascular complications, including myocardial infarction and stroke. The USPSTF found poor evidence to assess possible harms of screening. As a result, the USPSTF could not determine the balance of benefits and harms of routine screening for type 2 diabetes.

2. The USPSTF recommends screening for type 2 diabetes in adults with hypertension or hyperlipidemia. B recommendation.

The USPSTF found good evidence that, in adults who have hypertension and clinically detected diabetes, lowering blood pressure below conventional target blood pressure values reduces the incidence of cardiovascular events and cardiovascular mortality; this evidence is considered fair when extrapolated to cases of diabetes detected by screening. Among patients with hyperlipidemia, there is good evidence that detecting diabetes substantially improves estimates of individual risk for coronary heart disease, which is an integral part of decisions about lipid-lowering therapy.

Update Key and Subsidiary Questions

This report examines five Key Questions and three subsidiary questions, which were updated and revised from the prior report:[40, 76]

Update Key Question 1. Is there direct evidence that systematic screening for type 2 diabetes, IFG, or IGT among asymptomatic adults over the age of 20 years at high-risk for diabetes complications improves health outcomes? Does it improve health outcomes for asymptomatic individuals at average-risk for diabetes complications?

Update Key Question 2. Does beginning treatment of type 2 diabetes in adults early as a result of screening provide an incremental benefit in health outcomes compared with initiating treatment after clinical diagnosis?

Update Key Question 3. Does beginning treatment for IFG and/or IGT in adults early as a result of screening provide an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis of type 2 diabetes?

Update Key Question 4. What adverse effects result from screening an adult for type 2 diabetes or IFG/IGT?

Update Key Question 5. What adverse effects result from treating an adult with type 2 diabetes, IFG, or IGT detected by screening?

Subsidiary Question 1. What are the yields (accuracy and reliability) of different re-screening intervals among persons with an initial normal fasting glucose?

Subsidiary Question 2. What is the yield [accuracy, reliability, and prevalence] of screening for type 2 diabetes with A1c?

Subsidiary Question 3. Does beginning treatment for IFG or IGT early as a result of screening decrease the incidence of diabetes compared with initiating treatment after clinical diagnosis?

II. METHODS

This report updates the prior evidence review of 2003 by Harris and colleagues,[40, 76] using the evidence that the prior authors synthesized, adding to it data from new trials and updates from previously included studies. The revised Key Questions and the work plan for the review were developed collaboratively by the review team, Agency for Healthcare Research and Quality (AHRQ) officers, and the USPSTF topic leads. This report will form the evidence base from which the USPSTF will formulate recommendations.

Using the methods of the USPSTF[77] that are fully detailed in Appendix C, we modified the prior analytic framework and Key Questions to guide our literature search (Figure 2). The analytic framework depicts the relationship between screening a population at risk for diabetes complications and critical final health outcomes, and has been modified somewhat from the previous framework.[40] The current framework focuses on both populations at high and average-risk of diabetes complications, as well as on asymptomatic adults. The framework also explicitly encompasses IFG and IGT. We have added two final outcomes (quality of life and symptomatic neuropathy) and we focus here on only one intermediate outcome - incidence of diabetes (for prediabetes interventions), as this report is based primarily on final health outcomes.

We focus on the risk for complications from DM2 as the goal of screening is to improve health and well-being, which is contingent on decreasing the complications of DM2, and not primarily on decreasing the prevalence of the disease. We do not consider studies that exclusively enrolled persons with known cardiovascular disease (i.e., secondary prevention studies), as we consider those persons to have a complication from DM2. Because of the burden of cardiovascular disease in persons with diabetes and the overlap of risk factors for microvascular disease (i.e., hypertension), we consider persons with diabetes at risk for cardiovascular disease to be those at higher risk for DM2 complications. The risk factors identified as significant predictors of cardiovascular events amongst persons with DM2 include older age, smoking, hypertension, hyperlipidemia (specifically, an elevated total cholesterol/high-density lipoprotein [HDL] ratio), higher glycemic burden, and certain high-risk ethnic groups.[78]

We searched Medline and the Cochrane Library for systematic reviews and relevant studies published in English between March, 2001 (6 months prior to the cut-off for the prior search)

and July 2007. Our search strategies are contained in Appendix C1. For large trials included in the prior report,[40] we searched for related recent publications that presented additional data that fulfilled our inclusion criteria. We also examined the reference lists of key included studies and contacted experts for additional citations. We examined relevant systematic reviews retrieved from our searches, and for Key Questions, we evaluated all studies included in those reviews for potential inclusion in this report.

Titles and abstracts were screened (using inclusion criteria described in Appendix C2) by one author and a random sample of 1500 titles and abstracts were reviewed by two authors, giving a 5% margin of error on inter-rater reliability, assuming that both reviewers identified the same percentage of potentially relevant articles. Abstracts identified by one or both reviewers were retrieved in full-text format and reviewed in duplicate to determine inclusion status. Where there was disagreement between the two full-text reviewers, consensus was achieved through discussion.

Data were abstracted by one author and checked by a second. Key studies were reviewed and discussed by all authors. Quality assessment (internal validity) of individual randomized, controlled trials (RCTs) was performed by assessing factors that might introduce bias: adequate randomization, allocation concealment, baseline comparability of participants, blinding, and loss to follow-up (see Appendix C3). Studies were rated as good, fair, or poor quality. Potential applicability to widespread primary care practice was also assessed based on the approach to participant recruitment and selection in each study. The quality of cohort and case control studies was performed using the USPSTF approach,[77] again grading studies as good, fair, or poor. Pilot and cross-sectional studies were not assessed for quality. Systematic evidence reviews were rated as good, fair, or poor, using the methodology described in Appendix C4.

Modeling studies were identified from a our main search as well as from a recent, high-quality systematic review of DM2 screening by the National Health Service Research and Development Health Technology Assessment (HTA) Programme.[13] We independently abstracted the relevant studies included in their report and relied upon their extensive assessments of model quality.

A draft of the systematic review was reviewed by external peer reviewers (Appendix C5) from relevant professional organizations, federal agencies, and the private sector. Revisions were made based on these comments.

Statistical Analysis

We performed a meta-analysis to provide combined estimates of drug and lifestyle modification the effect of drug and lifestyle modification on reducing diabetes incidence. Most studies reported a hazard ratio (HR) and its standard error (SE) from a Cox regression. When HR was not reported[79-81] either a rate ratio standard error or risk ratio was calculated using reported data. Hazard ratio, rate ratio, and risk ratio could all be considered as a measure of relative risk (RR), and combined in the meta-analysis. For the Diabetes Reduction Assessment with Ramipril and

Rosiglitazone Medication (DREAM) trial,[82] a 2x2 factorial design was used, and HRs for both rosiglitazone and ramipril used data from all participants; therefore, the variance of the HR from each drug is multiplied by 2, so that result from each drug is down-weighted, and the DREAM trial receives appropriate weight as one study in the analysis.

Statistical heterogeneity was tested used the standard χ^2 test. The overall estimates of RR were obtained by a random effects model.[83] Estimates from the random effects model incorporate the variability among studies and represent a more conservative approach. When there is no heterogeneity among studies, both fixed and random effects model would yield same results.

III. RESULTS

See Appendix C6 for a literature flow diagram stratified by Key Question; excluded studies are catalogued in Appendix C7.

Update Key Question 1. Is there direct evidence that systematic screening for type 2 diabetes, IFG, or IGT among asymptomatic adults over 20 years of age at high-risk for diabetes complications improves health outcomes? Does it improve health outcomes for asymptomatic individuals at average-risk for diabetes complications?

Summary of Findings

There are no RCTs examining the effectiveness of a screening program for DM2. The prior review by Harris and colleagues[40, 76] identified no direct evidence provided by studies of any design addressing screening effectiveness. For this updated review, we identified three studies addressing this question. A small, case-control study did not find benefit from screening when microvascular complications were considered.[84] In a cross-sectional study, the prevalence of visual impairment and blindness was no greater in a population that had been screened for DM2 and for diabetic eye disease than in a matched, non-diabetic group.[85] In a poor-quality, cross-sectional study,[86] the prevalence of diabetic retinopathy was similar in persons with newly-diagnosed DM2 via a community screening program, and persons newly-diagnosed in general practice. The limited data from these studies do not provide sufficient direct evidence of the effectiveness of screening for DM2 in either targeted or general populations.

Recent high-quality modeling studies[13, 87] suggest that targeted screening for DM2 among persons with hypertension may be relatively cost-effective when macrovascular benefits of optimal blood pressure control are taken into account; also older persons benefit more than younger age groups. Waugh and colleagues also suggest that screening is more cost-effective among obese persons.[13]

The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study,[88] currently in progress, may shed light on differences in baseline characteristics and long-term health outcomes between persons with screen-detected DM2 and those who present with symptoms.

Study Details

To our knowledge, the effectiveness of a screening intervention for DM2 has not been tested to date in an RCT. In the ideal study, a population without diabetes or prediabetes would be randomized to either a screening intervention for DM2 or prediabetes, or to no intervention with usual care, when an individual presented with DM2. The screened population would be managed with usual care if they screened positive either for DM2 or prediabetes, and subjects would be followed for their lifetime for health outcomes. Such a study will not likely ever be performed because a large number of participants would have to be followed for long periods of time; case-finding and opportunistic screening for prediabetes and diabetes occur frequently in practice, using various diabetes risk factors for assessment; and laboratory panels, which include a plasma glucose, are commonly performed.

In the absence of trial data, we are left to consider: 1) direct evidence from studies comparing screening to no screening, but which are not RCTs; and 2) indirect evidence which examines various aspects of the relationship between screening and health outcomes. Key Questions 2 through 5 address various facets of the indirect evidence. Three studies in this updated review provide some direct evidence of the effects of a screening intervention on health outcomes; however, these data were not sufficient to determine the effect of screening directly.

A fair-quality, case-control study examined 303 cases of DM2 with one or more symptomatic, microvascular, diabetic complications matched 1:1 to control subjects (with or without DM2) (see Appendix B3 for study details).[84] The adjusted odds ratio (OR) for a history of screening at least once over a 10-year period compared to no screening, was 0.87 (95% confidence interval [CI], 0.38 – 1.98), suggesting that screening does not significantly reduce the risk of certain microvascular diabetic complications. The CI was wide, however, and was also consistent with a modest benefit.

In a Swedish community where systematic screening has occurred since 1983, Olafsdottir and colleagues[85] compared visual acuity and blindness in persons with known DM2 to vision in age- and sex-matched controls without diabetes, obtained from a national register. No significant differences were noted between these two populations in most measures of visual acuity, although more control subjects had visual acuity ≥ 1.0 (optimal vision) ($p<0.05$) (classification of the Los Angeles Latino Eye Study.)[89] Thus, in a population that had been screened for DM2

and for diabetic eye disease, the prevalence of visual impairment and blindness was no greater than in a matched, non-diabetic group. It was unclear in this study, however, how many subjects in the diabetes group were screen-detected versus presented with clinical symptoms, and the mean duration of known diabetes was 9 years. Given the presence of registries and an interest in diabetes in this community, standards of care for diabetes and diabetic eye disease may have been quite high. Thus, it is not possible to separate out the effects of DM2 screening specifically on the favorable eye outcomes.

In a poor-quality, cross-sectional study in rural and urban India,[86] diabetic retinopathy rates were compared between persons with newly-diagnosed DM2 via a community screening program who presented for retinopathy screening (n=173), and persons newly-diagnosed in general practice, who also presented for retinopathy screening (n=128). No significant differences were noted between the two groups in the prevalence of diabetic retinopathy, including sight-threatening retinopathy. Rates of retinopathy screening were only 15% for persons screened positive for DM2 in the community and were not reported for the subjects in the general practices. Thus, it is not possible to determine whether subjects examined in this study were representative of persons with newly-diagnosed DM2 in Indian communities, and these data are unlikely to be applicable to US populations and health care settings.

The in-progress ADDITION study[88] will provide important data on the effectiveness of treating persons with screen-detected diabetes (see Appendix B4 for details). In the first phase of the study, either targeted or community-based DM2 screening (depending on the location) will be performed, and the various outcomes examined among screen-detected persons include: cardiovascular risk profiles, psychological status, metabolic status, and costs. In the treatment phase of the study, persons with DM2 identified in the screening study will be randomized to conventional therapy or intensive multifactorial treatment focused on glycemic control and cardiovascular risk reduction, including aggressive blood pressure and lipid management. Primary endpoints at 5-year follow-up include mortality, cardiovascular events, and other health outcomes. This study is expected to be completed in 2009 (personal communication, Dr. T. Lauritzen, 1/26/07).

Modeling studies of screening interventions

In view of the paucity of data on the effectiveness of DM2 screening programs, we searched for studies modeling screening interventions using various simulation techniques. Models examining effectiveness and economic efficiency have been developed over the last 10 years. We identified seven studies modeling the effects of diabetes screening interventions,[13, 43, 87, 90-93] as well as a systematic review[13] (see Table 2; Appendix B5.) Modeling studies were not considered previously in the review by Harris and colleagues.[76] Modeling has also been used to examine the effectiveness of treatment of prediabetes and diabetes. Those studies will be discussed under Key Questions 2 and 3.

A recent HTA[13] systematically reviewed studies of economic models for screening for DM2 and prediabetes, and concluded that a good case could be made for targeted screening for both DM2 and IGT. Waugh et al suggest first an assessment of risk based on age, weight, and

hypertension, followed by a test of blood glucose, either fasting plasma glucose, OGTT or A1c, as none of these tests is ideal. They base their conclusions on the widespread availability of relatively inexpensive, effective prevention strategies for cardiovascular disease, particularly statins. Waugh et al concluded that targeted screening for DM2 is relatively cost-effective and they suggest that economic models to date may have underestimated long-term health benefits by not fully taking into account the effects of lifestyle interventions on reductions in various cardiovascular risk factors.

The first major publication of an economic model of diabetes screening was published by The Diabetes Cost-effectiveness Group at the Centers for Disease Control and Prevention (CDC), who developed a Monte Carlo simulation model to examine the effectiveness of a screening intervention[90] from the perspective of the health care system. The CDC group concluded that one-time opportunistic screening during a regular physician visit for persons 25 years of age or older produced significant gains in QALYs: 0.08 years all ages combined; 0.35 years for persons aged 25 to 34 years, with progressively fewer QALYs gained for each increased age grouping (e.g., 0.01 years for persons 65 years of age or older). The incremental gains in life-expectancy were higher for African Americans for all age groups. The cost per QALY was also lowest in the youngest age group and rose consistently with each decade of age, ranging from $56,649 per QALY for persons 25 to 34 years of age to $116,908 per QALY for persons 65 years of age and older. The screening intervention was more cost-effective in the younger population as they gained more life-years free of complications, despite higher screening costs per case detected.

This original CDC model[90] has become outdated; this model did not examine the effects of blood pressure or lipid control on life expectancy. Nor did the model examine the macrovascular effects of earlier glycemic control, as data to support that relationship were not available at the time of the publication (1998). This model has also been criticized for lack of transparency of some of the model components and assumptions, and for limited sensitivity analyses.[13]

Goyder and Irwig[91] developed a decision analysis of a mass screening intervention and included both microvascular and macrovascular complications for treatment and outcomes. They concluded that benefits of screening outweigh harms by 10 QALYs for every 10,000 persons screened. They did not include economic data, however, and this model has been criticized for not being transparent, for inadequate justification of assumptions, and a there is no reporting of validation of the model.[13]

Using a Markov model, Hofer and colleagues[92] examined a hypothetical American population with recent-onset DM2 under various scenarios. They found that with perfect screening (diagnosis at the onset of disease), and idealized treatment (A1c never rises above 9.0%), the rate of blindness was reduced by 71% compared to usual case-finding in a homogeneous population of persons with DM2-onset over age 40 years and A1c $\geq$ 12.0%. In a population of 1,000 persons with DM2 representative of an American population, the total benefit of universal screening and ideal treatment would be a reduction of about 30,000 cases of blindness. Screening would confer 7% of the benefit and improved treatment an additional 65%.

Chen and colleagues[43] developed a Markov Monte Carlo simulation model to examine cost-effectiveness of mass screening of a hypothetical Taiwanese population at 2- and 5-year intervals. They found that microvascular complications were reduced equally for the 2- and 5-year screening groups compared to the control group. The incremental costs per QALY were higher with screening every 2 years, compared to a 5-year interval. These authors concluded that mass screening was relatively cost-effective compared to opportunistic screening and to other commonly-implemented screening interventions. This model lacks transparency as presented in this publication: no sensitivity analyses were conducted, and macrovascular disease was not considered.[43]

Both macrovascular and microvascular complications were included in a more recent Markov model,[87] using data from the Hypertension Optimal Treatment (HOT) trial[94] which demonstrated that lower blood pressure targets improved cardiovascular outcomes among persons with DM2 and hypertension, as well as United Kingdom Prospective Diabetes Study (UKPDS) data[90] on the effects of intensive blood glucose control on microvascular complications. In this model diabetes screening targeted to persons with hypertension was more cost-effective than universal screening, and both targeted and universal screening of older persons were more cost-effective than screening of younger persons. For example, the cost per QALY compared to no screening for a 55 year old was $34,375 for targeted screening and $62,934 for universal screening. Most of the benefit of screening came from reducing coronary heart disease events by intensive control of hypertension, rather than from reducing microvascular complications. This model is an important advance on the prior modeling studies, incorporating data on glycemic control in DM2 from the UKPDS[90] and on intensive blood pressure control.[94] The model parameters were relatively transparent and adequately justified, although the model assumed 100% adherence and follow-up.[13]

Glumer and colleagues[93] modeled the effects of treatment for hyperglycemia, hypertension, and dyslipidemia combined, in screen-detected persons on cardiovascular events over 5 years. In their least conservative model with low costs and multiplicative risk reduction for combined treatments, the cost per event prevented was between £23,000 and £82,000. These authors noted that their model was most sensitive to assumptions about the effects of treatment and less sensitive to population characteristics.

The recent HTA of screening for DM2[13] reported their own model of the cost-effectiveness of screening, developed for United Kingdom populations. This transitional probabilities model based on UKPDS data suggests that screening for DM2 is relatively cost-effective for individuals 40 to 70 years of age, with a cost per QALY of £2,266 compared to no screening for the base-case population 40 to 70 years of age. This low cost-effectiveness ratio was due to both cost reductions and QALYs gained from reductions in complications, largely from fewer cardiovascular events due to statin use and fewer microvascular complications. Screening was somewhat more cost-effective in the older age groups (among persons 60 to 69 years of age, the incremental cost per QALY was £1,152) and in hypertensive and obese subgroups. Cost-effectiveness was determined more by assumptions about the degree of glycemic control, the effectiveness of other treatments on cardiovascular risk, and the low cost of statins, than by assumptions about the screening program.

Update Key Question 2. Does beginning treatment of type 2 diabetes early as a result of screening provide an incremental benefit in health outcomes compared with initiating treatment after clinical diagnosis?

Summary of Findings

We identified no studies that directly explored this question by comparing treatment effects between persons with screen-detected and clinically-detected diabetes, nor did we identify studies reporting treatment effects in an exclusively screen-detected diabetes cohort. Due to the absence of direct evidence, we examined studies of populations with mean duration of diabetes less than or equal to one year, as well as studies comparing treatment effects in diabetic versus nondiabetic populations.

There were no new completed studies examining the effect of glycemic control strategies in persons with newly diagnosed DM2 since the prior review. There is no clear evidence that persons with diabetes detected by screening would respond differently to specific antihypertensive regimens compared to persons without diabetes, though methodologic issues limit the robustness of this conclusion. Studies of intensive lipid-lowering treatment in persons with and without diabetes suggest that persons with diabetes benefit to a similar extent as those without DM2. The results are largely driven by one study in which the subgroup of persons with diabetes, regardless of initial low-density lipoprotein (LDL) cholesterol, benefited significantly from lipid-lowering treatment despite a lesser cardiovascular risk profile than the subgroup of persons without diabetes, many of whom had known coronary heart disease.[95] The studies of aspirin for primary prevention of cardiovascular events suggest that aspirin may not reduce the risk of myocardial infarction in persons with diabetes, but aspirin does seem to lower the risk of ischemic stroke in women with diabetes.[96, 97]

Modeling of diabetes interventions is a relatively young field and models vary in their perspectives, methods, and results. Three models suggest that aggressive blood pressure, lipid, and glycemic control may be effective and relatively cost-effective. However, their assumptions are all based on data from trials which included both clinically- and screen-detected persons with diabetes, and thus these models do not directly address the question of the cost-effectiveness of screening.

Study Details

Two types of evidence address the question of whether early treatment benefits screen-detected persons with DM2. (See Appendices B6 and B7 for details).

Does initiating treatment of diabetes, diabetes-complications, and cardiovascular disease risk factors in patients with newly-diagnosed DM2 improve health outcomes compared to treating clinically-detected patients?

No study has prospectively compared treatment effects between persons with screen-detected diabetes (either through mass or opportunistic screening) and those who were diagnosed after presenting with symptoms of hyperglycemia or with a diabetes-related complication (e.g., symptomatic ischemic heart disease, infected foot ulcer). The results of the ADDITION study,[88] discussed above, should help inform the question of the effectiveness of treatment for screen-detected persons with DM2.

We identified no new cardiovascular risk reduction studies which included persons newly diagnosed with diabetes. We examined a recent, high-quality systematic review of disease management interventions which included 66 studies, only one of which met our inclusion criteria. Most studies examined only intermediate outcomes or included persons with long-standing diabetes. The single relevant study randomized persons with screen-detected diabetes to usual care or a structured care intervention (a combination of scheduled chronic care visits, provider education, registry reports, and patient education) and found no significant difference in final health outcomes between the two groups.[98]

Would knowledge of a diabetes diagnosis prompt a change in management?

Tight glycemic control. There have been no new trials in persons with DM2 examining the effects of tight glycemic control. As discussed in the last review,[76] the UKPDS is the largest and most influential trial of tight glycemic control in persons with newly diagnosed DM2. The study provided some evidence that tight glycemic control was associated with a 25% reduction in microvascular complications – mostly due to a reduction in need for retinal photocoagulation - as well as a trend towards reduced cardiovascular events in obese persons with diabetes.[99] Intensive glucose control was not associated with high rates of hypoglycemia.[100] A recent meta-analysis combined results from older trials examined in the last USPSTF review[40, 76] and concluded that tight glycemic control resulted in a modest reduction of macrovascular events in persons with DM2.[37] This result was mainly driven by a reduction in peripheral vascular and cerebrovascular events, though examination of the individual trials showed largely nonsignificant results. It was unclear how overlapping populations from the UKPDS were accounted for in this meta-analysis.

It is unlikely that firm evidence of the final health benefits of early glycemic control from a controlled trial of a screen-detected population will ever be available because it would be unethical not to treat persons with known diabetes.[101] The ADDITION study should provide some valuable information, although the comparison group will be receiving usual care including glycemic control strategies; it will therefore be assessing the incremental benefit of very aggressive glycemic control over current standards for glycemic control in a screened population.

Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, also in progress, will compare intensive glycemic control strategies to more moderate glycemic targets (target A1c 6.0% vs 7.0 – 7.9%), though not specifically in a screened population (the average duration of diabetes in the trial population remains unclear).[102]

Specific antihypertensive treatment. Since the prior review, there were no new studies involving antihypertensive agents in screen-detected individuals, however we identified two new trials[103, 104] comparing the effect of different antihypertensive regimens in persons with and without diabetes (see Table 3), and one trial discussed in the previous report.[105, 106]

None of the comparative effectiveness trials suggested that persons with diabetes would clearly benefit from a specific antihypertensive drug compared to those without diabetes. However, none of the studies was originally powered to detect differences between the diabetes and non-diabetes subgroups. Furthermore, the demographic and cardiovascular risk profile characteristics were significantly different between the diabetes and non-diabetes subgroups, so it is unclear whether persons with diabetes with similar cardiovascular risk profiles as the overall trial population would experience differing treatment effects.

The largest of these trials was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study[103] which included over 15,000 persons with diabetes. Overall, this fair-quality study did not provide evidence that persons with diabetes would benefit from a particular antihypertensive drug more so than persons without diabetes. There were inconsistent and relatively small differences noted among the multiple treatment comparisons made across several subgroups. The lower risk of heart failure among those assigned to chlorthalidone was the only outcome that approached consistency across glycemic strata.[103] This study did not plan for a diabetes subgroup analysis *a priori*, so the study may have been underpowered to detect significant differences according to diabetes status. Moreover, the achieved systolic blood pressure at 5-year follow-up was significantly higher in those assigned to lisinopril than either amlodipine or chlorthalidone (137.9 mm Hg, 136.3 mm Hg, and 135.0 mmHg, respectively) in the diabetes subgroup.

The Losartan Intervention for Endpoint Reduction Trial (LIFE) study, covered in the previous review, which included persons with hypertension and left ventricular hypertrophy, showed persons with diabetes had lower cardiovascular mortality with losartan compared to atenolol, whereas those without diabetes experienced a reduction in stroke with losartan compared to atenolol.[105, 106] The Controlled Onset Verapamil Investigation of Cardiovascular Endpoints Trial (CONVINCE) trial compared verapamil to either a beta-blocker or thiazide diuretic-based regimen; there was no evidence of differential effect of treatment on cardiovascular outcomes between those with and without diabetes.[104]

We identified one meta-analysis of antihypertensive trials which compared outcomes between persons with and without diabetes.[107] Angiotensin-receptor blockers (ARBs) provided greater protection against congestive heart failure for those with diabetes than those without diabetes (p=0.002). Angiotensin converting enzyme (ACE) inhibitors seemed to offer more protection

against cardiovascular death (p=0.05) and total mortality (p=0.03) for those with diabetes than without diabetes. However, all of the studies of ACE inhibitors compared to placebo were secondary prevention trials, except for the Heart Outcomes Prevention Evaluation (HOPE) trial, which was a combination of primary and secondary prevention.

The HOPE trial, discussed in the last review, did show that those with DM2 and one additional cardiovascular risk factor experienced a 25% risk reduction in cardiovascular events, cardiovascular mortality, and stroke with ramipril treatment – a similar benefit as those with a history of ischemic heart disease and no diabetes. Of interest, those with diet-controlled diabetes seemed to derive a more substantial benefit from ramipril than those on insulin, perhaps suggesting those with less advanced diabetes benefited more from treatment, although this conclusion was made in the context of multiple comparisons.[108, 109]

Of note, we excluded from our review two large RCTs published in 2001 which examined the role of the ARBs losartan and irbesartan in slowing progression of nephropathy in patients with DM2.[110, 111] There was a 25-33% risk reduction in the doubling of the serum creatinine, and losartan was associated with a 28% risk reduction in the incidence of end-stage renal disease. Both trials were excluded because they enrolled persons with advanced diabetes and nephropathy at baseline and, therefore, did not address the issue of the benefits of early detection and treatment of diabetes.

Intensity of antihypertensive treatment. The previous USPSTF review[40, 76] found good evidence that aggressive blood pressure control in persons with diabetes reduces cardiovascular morbidity. The most influential study was the HOT trial in which the diabetes subgroup experienced a 51% relative risk reduction in cardiovascular events from more aggressive blood pressure control, a greater benefit than observed for non-diabetic patients.[94]

We did not find any new trials comparing intensive and less intensive blood pressure treatment targets in persons with and without diabetes. A recent meta-analysis presented limited evidence that higher intensity antihypertensive treatment reduces the risk of major cardiovascular events in persons with diabetes, but not in those without diabetes.[107] The differential effect on cardiovascular mortality was less clear. The four studies contributing to the diabetes subgroup meta-analysis were all reported in the last review.[94, 112-114]

The ACCORD trial, as described above, will also examine the relative benefits of very intensive blood pressure control as compared to more moderate standards (target systolic blood pressure < 120 mmHg vs < 140 mmHg).[102]

Initiation of lipid-lowering treatment. At the time of the last review, there were no primary prevention trials with large numbers of participants with diabetes yet published. Secondary prevention trials including persons with diabetes and coronary heart disease had shown risk reductions ranging 19-42% in the incidence of recurrent cardiovascular events.

We identified four new trials and one meta-analysis examining the effects of lipid-lowering treatment in persons with and without diabetes (see Table 4). All of the trials examined the efficacy of HMG CoA reductase inhibitors in primary prevention of cardiovascular events and mortality. In one of the trials, neither the diabetes nor the non-diabetes subgroups benefited from statin treatment, but there was a high rate of non-study statin use in the control group, and the differential reductions in LDL cholesterol achieved were relatively small.[115] In two fair-quality trials, statin therapy did not significantly reduce the primary endpoint (coronary events in the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT] trial and coronary events plus stroke in the Prospective Study of Pravastatin in the Elderly at Risk [PROSPER] trial) in the diabetes subgroup, but did benefit the non-diabetes subgroup.[116-118] Comparisons between persons with and without diabetes were hampered by a relatively low absolute number of events in the diabetes subgroup. The findings of the PROSPER study, which showed a trend towards increased risk of coronary events and stroke in the statin group amongst persons with diabetes, are puzzling, but this study also had the lowest number of persons with diabetes.[117]

The Heart Protection Study (HPS)[95] was a large, good-quality RCT examining the efficacy of an HMG CoA reductase inhibitor in primary and secondary prevention of cardiovascular events and mortality. Persons with diabetes and without a history of vascular disease experienced a similar reduction in cardiovascular events as persons without diabetes who had known vascular disease (27% relative risk reduction, $p < 0.001$ in both groups). A detailed subgroup analysis of the 5,963 persons with diabetes revealed that risk reduction was similar among various subgroups, regardless of duration of diabetes, presence of treated hypertension, or initial LDL cholesterol. Although it appeared that persons with shorter diabetes duration benefited to a similar extent as those with much longer standing diabetes, there was not sufficient power to determine if newly-diagnosed (i.e., less than 1 year) participants benefited to a significant extent.

A recent meta-analysis included six primary prevention trials, including the four discussed above along with an older trial using a fibric acid derivative and an older statin trial which reported analyses of the subgroup of participants with diabetes.[119] Overall, lipid lowering drug treatment appeared to be equally efficacious in persons with and without diabetes. However, there was significant heterogeneity among the trials. The HPS contributed the largest number of persons with diabetes to the analysis, and also yielded the highest risk reduction.[95] Of note, the risk difference was significantly higher in secondary prevention trials, likely reflecting the much higher event rates. Excluding the fibrate trial yielded an almost identical risk reduction to the overall effect of the six studies, likely reflecting the very small number of persons with diabetes in fibrate trial.

Aspirin for primary prevention. The last review included a large meta-analysis of aspirin use in the prevention of cardiovascular events and stroke in high-risk patients, including over 5,000 persons with diabetes. This Antithrombotic Trialist's Collaborative meta-analysis showed a 7% risk reduction of borderline significance in the incidence of vascular events amongst diabetics.[120] The meta-analysis was mainly driven by the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) trial which showed a 17% relative risk reduction in the incidence of fatal and non-fatal coronary events (95% CI, 0.66 – 1.04).[121] The Physicians Health Study showed that

the use of aspirin was associated with a significant cardiovascular risk reduction in persons with diabetes.[122]

Since the prior review, we identified two new studies of low-dose aspirin use for primary prevention of cardiovascular events in persons with and without diabetes.[96, 97] In the Primary Prevention Study, the nondiabetes subgroup experienced a 41% relative risk reduction (95% CI, 0.37 – 0.94) in the incidence of major cardio- and cerebrovascular events, while the subgroup of persons with diabetes did not derive any benefit.[96] This fair-quality study was stopped early with a resultant low event rate in both groups. Given the small size of the groups with diabetes, the trial was likely underpowered to detect a difference in this group. Another large trial of good quality showed that aspirin did reduce the incidence of ischemic stroke in women with diabetes,[97] and there was no evidence that the effect of aspirin was significantly more pronounced in diabetic women than those without diabetes. The difference in results from the Primary Prevention Program[96] may be due to differences in the populations considered and perhaps in the differential risks for stroke versus myocardial infarction (the rate of stroke was actually higher than the rate of myocardial infarction in the Women's Health Study[97]).

Modeling studies of treatment of diabetes

In addition to examining the effects of screening interventions, economic models have also been used to examine the effects of treatment of persons newly-diagnosed with DM2.[123-126] Several additional models are reported to be under development (The Cardiff Diabetes Model of newly-diagnosed type 2 patients and the Sheffield Diabetes Model).[127] The CDC Diabetes Cost-effectiveness Group estimated the incremental cost-effectiveness of intensive glycemic and blood pressure control as well as the use of pravastatin to reduce total cholesterol in persons newly-diagnosed with DM2.[123] This model assumed that intensified blood pressure control did not have an effect on coronary heart disease (based on UKPDS data[112]). Intensive blood pressure control and reduction of serum cholesterol increased QALYs by more than intensive glycemic control (see Table 5 and Appendix B8). Blood pressure treatment was, in fact, cost saving.

In the Center for Outcomes Research (CORE) model, Palmer and colleagues[124, 128] examined hypothetical interventions that led to 10% improvements in one or more of A1c, systolic blood pressure, total cholesterol, or HDL. The costs of interventions were not included in this model. They noted an increase in quality-adjusted life expectancy of 1.7 years with improvements in all four parameters, and the lifetime costs of complications decreased the most with improvements in all four. As a single intervention, costs improved the most with A1c improvement (costs decreased by $10,800).

The UKPDS Outcomes Model[125, 129-131] examined the lifetime economic efficiency of intensive blood glucose control compared to conventional control, with metformin therapy given to a subgroup who were more than 120% of ideal body weight. This model found that the most QALYs gained were with metformin therapy and the probability of being cost-effective at a ceiling ratio of 20,000 pounds per QALY was also greatest with metformin therapy in the overweight subgroup. In a comparison of conventional glucose control versus intensive control with a sulphonylurea or insulin,[132] the incremental cost per event-free year gained was £1166.

The Global Diabetes Model examined the effects of intensive lipid management in a staff-model health maintenance organization but does not provide comparison data for persons without such treatment (the comparator was another model).[126, 133]

Update Key Question 3. Does beginning treatment for IFG and/or IGT early as a result of screening provide an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis of type 2 diabetes?

Summary of Findings

A number of studies suggest that intensive lifestyle and various pharmacotherapeutic interventions decrease the incidence of DM2 over follow-up periods up to 7 years. There are few data on the prevention or delay of cardiovascular and other long-term health outcomes, including death. There are also very few data on treatments for cardiovascular risk factors among persons with prediabetes compared to normoglycemic populations. There is thus little direct evidence that identifying persons with prediabetes by screening will lead to long-term health benefits. Several high-quality modeling studies suggest that screening and treatment of prediabetes with a lifestyle intervention or metformin is relatively cost-effective, although the cost-effectiveness ratios vary widely depending on the assumptions used in the model.

Study Details

Evidence addressing several different questions informs the issue of whether the identification of persons with either IFG or IGT provides long-term health benefits compared to waiting until clinical presentation of DM2.

Does initiating treatment of dysglycemia or other cardiovascular risk factors among persons with prediabetes improve health outcomes compared to treating clinically-detected or screen-detected DM2?

If treatment of persons with prediabetes reduces diabetes-related complications compared to waiting until the onset of DM2 (screen- or clinically-detected), this would suggest that identifying persons with prediabetes is beneficial. In the prior USPSTF review, Harris and colleagues[40, 76] identified five trials[134-138] of lifestyle or drug interventions among persons with

prediabetes, three of which reported a reduced incidence of DM2 between 42% and 58% over 3 to 6 years with an intensive lifestyle intervention compared to usual care.[76] None of these studies examined cardiovascular outcomes, however, and none compared the treatment of prediabetes to clinically-unscreened diabetes.

We identified additional data published since 2003 that examined the effect of interventions on the incidence of diabetes or on long-term health outcomes among persons with prediabetes (see Table 6 and Appendix B9).[79-82, 136, 138-161] Two of these studies were included in the prior report, with more recent data published on cardiovascular outcomes.[140, 159] Two recent reviews examined the effectiveness of interventions to prevent or delay diabetes among persons with IGT;[162, 163] all English-language studies included in that review, save one, are included in this report or in the prior review.[76] One study contained in the review by Gillies and colleagues was not reviewed in the prior USPSTF review: a small study by Wein and colleagues[164] who compared an intervention group given 3-monthly telephone contacts with a dietician to a comparison group that received routine dietary advice. In this study the intervention group had a nonsignificant decrease in the risk of diabetes. This intervention was much less intense than the interventions included in both this review and the prior one.[76]

In the Diabetes Prevention Program (DPP)[79] an intensive lifestyle intervention and treatment with metformin both reduced the incidence of diabetes at 3-year follow-up. Neither the cumulative incidence of cardiovascular disease nor the event rate was different among treatment groups, however, the study was not adequately powered to examine these outcomes.[140] The DPP screened participants based on risk factors such as obesity, age, and family history and found that older age and higher BMI increased the yield of screening, and this was true across ethnic groups.[145]

In the Study to Prevent Non-insulin-dependent Diabetes Mellitus (STOP-NIDDM) trial, subjects with IGT were randomized to placebo or acarbose.[158] The cumulative incidence of DM2 was reduced significantly over the 3.3-year intervention (HR 0.75 [95% CI, 0.63 - 0.90]). Cardiovascular events of any type were also reduced (HR 0.51 [95% CI, 0.28 - 0.95] with an absolute risk reduction [ARR] of 2.5%) as was the development of hypertension (HR 0.66 [95% CI, 0.48 -0.89] with an ARR of 5.3%).[159] The number-needed-to-treat to prevent one cardiovascular event in persons with IGT was 40 over 3.3 years. This study was limited by an attrition rate of 24% overall, with a much higher rate in the treatment group.

A third trial presented cardiovascular outcomes. In the DREAM trial,[82] the primary composite outcome of cardiovascular events was not significantly different between the rosiglitazone and placebo groups (HR 1.37, 95% CI, 0.97 – 1.94). Rosiglitazone reduced the incidence of DM2 among persons with IFG and/or IGT when treated for a median of 3 years.[165] Ramipril was not effective in reducing the incidence of DM2, although 2-hour post load plasma glucose was significantly lower in the ramipril group (p=0.001).[82]

The Finnish Diabetes study,[138] included in the prior review, provided longer-term follow-up of a lifestyle intervention and found that the cumulative incidence of DM2 was significantly reduced at a mean follow-up of 3.2 years (HR 0.4 [95 % CI, 0.3 to 0.7; p<0.001]).[153] This was maintained 3 years after completion of the intervention (HR 0.57 [95% CI, 0.43 - 0.76]).[153]

In addition, two smaller trials were identified which examined the effect of lifestyle and pharmacotherapy interventions on incidence rates of DM2 among persons with prediabetes, and found a significant decrease in incidence compared to usual care.[81, 154] On the other hand in a third study, Watanabe and colleagues found no difference in diabetes incidence at 1 year with a dietary intervention, although the study was not powered for that outcome.[155] Pharmacotherapy has also been demonstrated to decrease progression to DM2. In the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study (rated fair-to-poor quality), orlistat produced a relative risk reduction in the incidence of DM2 of 45% over 4 years (although attrition rates were high)[161] and a meta-analysis of three other orlistat studies produced similar results.[80] Acarbose[156] and metformin[154] have also been shown to in decrease diabetes incidence at up to 3-year follow-up.

A pooled estimate for the relative risk reduction in the incidence of DM2 was 0.48 (95% CI, 0.40, 0.58). Pharmacotherapeutic interventions were heterogeneous (p-value- 0.001, Chi-square test for heterogeneity), with a pooled estimate of 0.65 (95% CI, 0.51, 0.83). Removal of the rosiglitazone arm of the DREAM trial[82] produced a homogeneous data ($p>0.05$, Chi-square test for heterogeneity) (see Figure 3).

We identified two studies of interventions in persons with prediabetes that are currently in progress and for which no published results are available. The Canadian Normoglycaemia Outcomes Evaluation (CANOE) trial[166, 167] focuses primary on whether treatment with metformin plus rosiglitazone, combined with a healthy lifestyle, will prevent the development of DM2 among persons 30 to 75 years of age with IGT over 4-year follow-up.

The National Type 2 Diabetes Prevention Program in Finland (Fin-D2D)[168] involves strategies to screen high-risk persons for prediabetes and diabetes followed by appropriate lifestyle and clinical interventions if they screen positive. The goals are to reduce the incidence of DM2 and to identify persons with undiagnosed DM2.

Are there different treatment targets for cardiovascular disease risk factors (hyperlipidemia, blood pressure) for persons with prediabetes compared to normoglycemic persons?

We did not identify any data to address this question.

Are there different medications for the treatment of hyperlipidemia, hypertension, and cardiovascular disease among persons with prediabetes compared to normoglycemia?

The only comparative effectiveness study involving persons with prediabetes was the ALLHAT trial,[103] which compared various antihypertensive therapies among persons with diabetes, IFG, and normoglycemia. Overall, the authors concluded that they failed to demonstrate superiority for an ACE-inhibitor or a calcium channel blocker compared with a thiazide-type diuretic across the three glycemic strata for the composite outcome of coronary heart disease death and nonfatal

myocardial infarction. In the setting of multiple comparisons, the relative risk of fatal coronary heart disease or non-fatal myocardial infarction was 1.73 (95% CI, 1.10 – 2.72) for participants assigned to amlodipine compared to chlorthalidone among persons with IFG; these drugs did not produce significant effects on this outcome among persons with DM2 or normoglycemia.

Modeling studies of treatment of prediabetes

Modeling studies have also been used to examine the treatment of prediabetes (see Table 7 and Appendix B10).[128, 169-177] The HTA[13] discussed in Key Question 1 systematically reviewed economic modeling studies of prediabetes treatment, and recommended screening for glucose intolerance because there are effective strategies for reducing cholesterol and blood pressure, and because DM2 can be prevented. These authors noted that although existing models were of variable quality, structure, and assumptions, all predicted that delaying the onset of diabetes would substantially reduce the incidence of vascular complications, improve quality of life, and avoid future medical costs. The authors concluded that if a screening program was implemented to target persons at risk for diabetes, subsequent treatment of persons with IGT with lifestyle or pharmacologic interventions was a good use of resources. Waugh and colleagues appear to assume that the effects of treating persons with screen-detected diabetes are the same as for treating clinically-detected populations, and that there are proven linkages between treating dysglycemia and final health outcomes. All modeling studies included in the HTA are reviewed herein.

Herman and colleagues[172] examined the life-time utility and cost-effectiveness of the DPP lifestyle intervention.[79] They noted the intervention to be relatively cost-effective (cost/QALY, $8,800 from a societal perspective), with gains in life expectancy of 0.5 years and a decrease in the incidence of diabetes by 20%. Results were somewhat less marked with metformin, but this treatment was still relatively cost-effective.

Eddy and colleagues[169] also examined the DPP interventions, using their Archimedes model.[170] Consistent with the model used by Herman and colleagues,[172] the Archimedes model predicted large absolute reductions in the proportion of persons developing DM2, a delay of 7 to 8 years in onset of DM2, and that the DPP lifestyle intervention leads to fewer complications and improved QALYs.[175] Eddy and colleagues, however, estimated much higher marginal cost-effectiveness ratios than did Herman et al.[172] For example, the cost per QALY of the lifestyle program compared to no intervention was $62,600 from a societal perspective in the Archimedes model and $8,800 in the CDC model. Differences between the two models included a longer time horizon for the CDC model, different assumptions about glycemic progression, and lower microvascular and macrovascular disease rates in the Archimedes model.[175]

Four Markov models evaluated primary prevention of DM2 among persons with IGT.[173, 174, 176, 177] All demonstrated relative cost-effectiveness of lifestyle interventions, and two models examining metformin also found cost savings under many conditions.[174, 176] The models of Segal and colleagues[173] and Caro and colleagues[174] were criticized by the HTA authors[13] for lacking transparency of the model inputs and assumptions. The Palmer and colleagues' model[176] was relatively transparent, but did not model individual complications.[13]

Update Key Question 4. What adverse effects result from screening a person for type 2 diabetes or IFG/IGT?

Summary of Findings

Data are sparse on the psychological effects of screening for DM2, and none of the available data suggested significant adverse effects at up to 1-year follow-up. In addition, no study reported serious, long-term, adverse effects of a new diagnosis of DM2 over a wide variety of outcomes including anxiety, depression, well-being, overall mental health, health-related quality of life, self efficacy, self care, and diabetes-related symptom distress.

Study Details

The previous review[40, 76] of the adverse effects of screening for DM2 identified no relevant studies, but suggested that labeling and false-positive diagnosis were potential effects that may lead to anxiety and other psychological distress, as well as changes in self-perception. In addition, the prior review suggested that false positive test results could lead to unnecessary treatment.

The negative psychological and physical effects of screening for, or receiving a new diagnosis of, DM2 or prediabetes was examined for this update (see Table 8 and Appendix B11 for further details).[178-190] Several studies were derived from the large observational study of the Dutch population (the Hoorn study)[178-181] The ADDITION trial, discussed previously, also contributed relevant data.[189, 190]

Effect of a false positive test for DM2 or prediabetes

We identified no studies that addressed the effects of a false positive result from any of the tests used to screen for dysglycemia. While false positive results can occur with a single fasting blood glucose test, the specificity of a single test is 95%.[76]

Labeling of a person as having DM2 or prediabetes

We identified no studies that directly addressed labeling of persons with screen-detected diabetes.

Psychological effects of screening

In the ADDITION study,[190] step-wise screening had limited effects on anxiety levels at up to 1-year follow-up. Being required to return for additional tests after an initial positive random blood glucose had a small, negative psychological impact of doubtful clinical significance. After notification of a positive screening test, subjects reported poorer health, higher anxiety, more depression, and more diabetes-specific worry (p all ≤ 0.05) than those with a negative test.

In a cross-sectional study at the time of screening for DM2 with an OGTT, Skinner and colleagues did not find that screening high-risk patients was associated with significant anxiety.[187] In a small, qualitative study of a stepped approach to screening,[181] screening was generally perceived positive and not burdensome. A minority of subjects had concerns about privacy, completing the risk factor questionnaire, and the inconvenience of the OGTT.

Siblings of patients with DM2 who did not have diabetes had slightly elevated anxiety levels (compared to normative values) at the time of screening with a fasting plasma glucose. Anxiety levels decreased at one year but remained above normal levels. Subjects with normal and with elevated glucose levels had similar anxiety levels and measures of well-being at baseline and 1-year follow-up.[183]

Psychological effects of the diagnosis of DM2

No study reported serious psychological or other adverse effects of a new diagnosis of DM2.[178-182, 185, 186, 188-190] Several studies compared persons with screen-detected DM2 to persons without diabetes. Adriaanse and colleagues,[180] using Hoorn observational data, at 2-week follow-up found no significant differences in well-being and health-related quality of life (HRQoL) (measured with the Short Form-36 [SF-36]) between newly-diagnosed subjects and those at high risk that screened negative. Scores were lower (poorer quality of life) for several SF-36 subscales in the group with diabetes at 6 months. At 1-year follow-up, however, no significant differences were noted. Also using Hoorn observational data, persons with screen-detected DM2 reported significantly more hyperglycemic and fatigue symptoms in the first year following diagnosis of DM2 compared to screened-negative persons.[179] However, total symptom distress was low and not significantly different between the two groups at up to 1-year follow-up. Edelman and colleagues[182] also found no significant differences between persons screened positive for DM2 and those screened negative using the physical and mental component scales of the SF-36 at 1-year follow-up. Similar results were noted by Nichols and Brown[185] who compared subjects with a fasting blood glucose between 126 and 140 mg/dl, who became diabetic after the change in definition in 1997,[191] to persons without DM2. They found that physical function was already lower in persons who met the new diagnosis of DM2, but the mental health component score was not different between the groups. This study also compared persons who were told of their new diagnosis of DM2, and those who had the disease but were

not yet informed of it. There was no difference between these groups in either the physical or mental health score at 1 year from the first questionnaire. Response rates were low, however, both at baseline (69% for both the DM2 and comparison groups) at 1-year follow-up (44%).

The ADDITION study of screen-detected DM2 in the Netherlands provides additional insight into the effect of screen-detected disease (based on stepped-screening using risk factor assessment, FPG, and OGTT) on various outcomes.[188-190] Thoolen and colleagues,[188] with response rates of 35% to 62%, found that persons with screen-detected diabetes generally reported low emotional distress and threat perceptions, high self-efficacy, but low self-care behavior. Intensively-treated patients reported more distress and less self-efficacy in the first year after diagnosis compared to usual-care patients, but the latter group experienced relatively more distress and less self-efficacy 2 to 3 years after diagnosis. In a qualitative study of reactions after a new diagnosis of DM2, patients tended to downplay the importance of the diagnosis and all had plans to control the disease.[189]

In a pilot study of the Hoorn cohort,[181] Adriaanse and colleagues found that persons with newly screen-detected DM2 did not experience the disease as "severe," although many perceived the need for a major change in their lifestyle.

One study compared newly-diagnosed persons with DM2 (76% of whom presented with clinical symptoms) identified in general practice with persons detected through a targeted population screening program.[178] The general practice group had significantly lower scores on mental health-related subscales of the SF-36 compared to the screen-detected group shortly after diagnosis; these differences persisted at 1-year follow-up. The general practice group, however, improved in perceived general health, and vitality scores improved over time, compared with the screen-detected group. This suggests improvements with treatment or adaptation to the disease. Perceived burden of diabetes-related symptoms improved significantly within the general practitioner group over the first year after diagnosis, ($p<0.001$) but did not improve in the screen-detected group ($p=0.093$). Symptom scores were higher (more symptoms) initially in the general practice group, but no differences were demonstrated at 1 year.

Psychological effects of a diagnosis of prediabetes

In the only study examining the effect of a diagnosis of prediabetes,[189] many study participants were confused by this diagnosis, and most were unconcerned and unaware of this diagnosis as a risk factor for DM2 or cardiovascular disease.

Update Key Question 5. What adverse effects result from treating a person with type 2 diabetes, IFG, or IGT detected by screening?

Summary of Findings

Recent systematic reviews of the adverse effects of drugs used in the treatment of DM2 and prediabetes reveal some significant new data related to the safety of thiazolidinediones. New information on an association between rosiglitazone and an increased risk of myocardial infarction was recently published.[192] For other drugs examined in studies included in Key Questions 2 and 3 in this review, we identified no new data on severe or idiosyncratic side effects in our systematic search when compared to data available at the time of the prior USPSTF review.[40, 76] Relatively common side effects such as cough with ACE-inhibitor and gastrointestinal effects with acarbose are a consideration when prescribing these drugs, but are not associated with increased mortality or adverse cardiovascular outcomes.

Study Details

We identified 24 recent systematic reviews[193-218] examining the adverse effects of drugs used in studies included in Key Questions 2 and 3 (see Table 9). For acarbose, a recent review noted no difference in mortality between treatment and placebo groups, however, there were significantly more side effects with acarbose than with than placebo (OR 3.37 [95% CI, 2.60 to 4.36]),[194] particularly gastrointestinal effects (OR 3.5, 95% CI, 2.7 – 4.4).[193] Pooled trial data for over 47,000 patients identified no cases of fatal or nonfatal lactic acidosis with metformin.[206] In another meta-analysis of metformin, there were no differences between the treatment group and a diet or placebo group for hypoglycemia or all-cause mortality.[205] Rates of hypoglycemia generally did not differ between treatment and control groups in a review of a broad spectrum of oral agents, except for sulfonylurea where rates were generally higher in the treatment group.[203] Gangji and colleagues found that glyburide caused more hypoglycemia than other sulfonylureas, but was not associated with an increased risk of cardiovascular events or death.[204]

ACE-inhibitors did produce a significant increase in cough compared to placebo (RR 3.17 [95% CI, 2.29 - 4.38]); and angiotensin II receptor antagonists also produced an increase in cough (two studies, RR 4.93 [95% CI, 1.00, 24.35]).[219] Myocardial infarction rates did not differ significantly between angiotensin II receptor antagonists and placebo; and cardiovascular disease mortality was slightly decreased compared with placebo (OR 0.91, 95% CI 0.83 – 0.99).[199] Exposure to angiotensin II receptor antagonists during the first trimester of pregnancy appears to be associated with an increased risk for adverse fetal outcomes (p=0.04).[198] Beta-blockers were associated with more withdrawals due to adverse events compared to placebo (RR 2.34 [95% CI, 0.84-6.62]), but cardiovascular mortality and stroke were significantly lower in the treatment group, and there was no difference between treatment and comparisons groups in total mortality.[202] The risk of any adverse events is elevated for statins (OR 1.4, 95% CI, 1.09 – 1.80), however the rates of serious adverse events were similar between the statin and placebo

groups.[212] Statin therapy was associated with a significant reduction in the risk of clinical cardiovascular events (OR 0.74, 95% CI, 0.69 – 0.80).[212] The incidence of rhabdomyalysis was low in persons taking statins (with the exception of ceruvistatin), and myopathy attributed to statins was also rare (11/100,000 person-years, excluding ceruvostatin).[211] The risk of cancer was not elevated with pravastatin (RR 1.06, 95% CI, 0.97 – 1.14).[209]

Recently published data on thiazolidinediones raise concerns about the safety of these drugs. A meta-analysis[192] (which was not a systematic review) suggested an increased cardiovascular risk associated with rosiglitazone compared to alternative oral diabetes therapies. A subsequent interim analysis of a multi-center, open-label RCT was inconclusive regarding the effect of this drug on overall risk of hospitalization or cardiovascular death, and the data were insufficient to determine whether rosiglitazone was associated with an increase in the risk of myocardial infarction.[220] Recent Cochrane reviews suggest that rates of edema were significantly increased with both pioglitazone[215] and rosiglitazone.[214] Pioglitazone was associated with a significantly increased rate of heart failure compared to placebo in another recent systematic review.[213] In a systematic review published after our final searches were complete, Singh and colleagues[216] found that among persons with IGT or DM2, rosiglitazone use for 12 or more months was associated with a significantly increased risk of myocardial infarction and heart failure, although the risk of cardiovascular mortality was not increased. Analysis of individual time-to-event data obtained from the drug's manufacturer suggested a lower risk of death, myocardial infarction, or stroke with pioglitazatone than with placebo or active comparator.[221] Serious heart failure was increased, but associated mortality was not. In a Cochrane review of pioglitazone,[215] only one study examined all-cause mortality[222] which was not significantly different between the intervention and placebo groups. In a Cochrane review of rosiglitazone, no study included mortality as a primary or secondary endpoint.[214]

IV. DISCUSSION

The ultimate goal of screening is to identify individuals who would not have otherwise come to clinical attention, and who would experience improved health outcomes from the initiation of a specific treatment after diagnosis. Screening for hyperglycemia can identify persons with undiagnosed diabetes or those at risk for developing diabetes and classified as having prediabetes. The treatments prompted by diagnosis and addressed by the studies in our review include lifestyle interventions, the use of hypoglycemic agents, and cardiovascular risk reduction mainly through blood pressure and lipid control strategies.

As yet, there is no direct evidence that clearly determines whether or not screening asymptomatic individuals for diabetes or prediabetes alters final health outcomes. There is evidence both from the prior review,[76] and from this update, showing that persons with diabetes who are at risk for

cardiovascular disease do benefit from aggressive blood pressure lowering and lipid-lowering therapy, although this has not yet been demonstrated in screen-detected individuals. Persons with newly-diagnosed, largely clinically-detected diabetes, derive benefit from intensive glycemic control largely from a reduction in microvascular events.[223] There is also evidence that in persons with prediabetes – an implicitly screen-detected population – intensive lifestyle modification likely delays the progression to clinical diabetes, although there is uncertainty about the ultimate benefit of such treatment in altering the natural history or improving final health outcomes.

The Outcomes Table (Table 10) shows the number-needed-to-screen (NNS) to prevent an outcome of interest in different theoretical populations. The NNS to prevent one case of blindness in one eye, or one cardiovascular event from aggressive blood pressure control over 5 years, has not changed from the prior estimates of Harris and colleagues,[76] as no new data on the effectiveness of these interventions were identified in this review. As noted previously,[76] interventions that target cardiovascular events produce greater effects than those targeting microvascular complications, which occur later in the disease process.

Using data from the HPS[95] on the effects of tight lipid control on cardiovascular outcomes, estimates of the NNS to prevent one cardiovascular event are similar to estimates from aggressive blood pressure control estimated from the HOT trial;[94] however given the lack of clear differential benefit of lipid-lowering therapy between the diabetic and non-diabetic subgroups in the HPS, these NNS estimates should be interpreted with caution.

Estimates of the NNS to delay one case of diabetes using an intensive lifestyle intervention based on the DPP[79] and the Finnish Diabetes Study[138] (i.e., to prevent one case over the duration of follow-up) are relatively favorable; screening 1,000 persons with prediabetes will delay 44 cases of DM2 over 3.0 years. Pharmacotherapy with metformin produced somewhat less favorable NNS, as the relative risk reduction was not as great as with the lifestyle intervention.[79] As with the prior review,[40, 76] there remain a number of important assumptions underlying the estimates of NNS, including length of the asymptomatic period, prevalence of undiagnosed diabetes or prediabetes, incidence rates of diabetes complications, and the treatment effect.

The yield of screening depends on a number of factors. Screening targeted to populations at risk for diabetes would likely increase the yield and efficiency of a screening program; a variety of risk scores have been developed to identify those at high risk for developing diabetes.[150, 224-228] In the DPP, older age and higher BMI increased the yield of screening, and this was true across ethnic groups.[145] On the other hand, the prevalence of diagnosed DM2 in certain high-risk groups such as non-Hispanic blacks and Mexican Americans has increased, while the proportion of those with undiagnosed disease in those groups has fallen, suggesting that opportunistic screening targeted to populations at high risk may already be occurring. This trend reduces the prevalence of undiagnosed DM2 and increases the NNS to prevent adverse events in the remaining unscreened group.[2]

Targeting Persons at High-risk for Complications from Diabetes

The yield of screening for diabetes and prediabetes is likely to increase if targeted towards groups at higher risk of complications from diabetes. As noted previously,[76] interventions that target cardiovascular events produce greater effects than those targeting microvascular complications which occur later in the disease process.

Would the diagnosis of diabetes or prediabetes identify individuals who would benefit from aggressive macrovascular risk reduction strategies and who would not have been otherwise identified through hypertension and hyperlipidemia screening protocols, based on current recommendations?[75]

The current USPSTF guidelines recommend screening for diabetes in persons with hypertension or hyperlipidemia. The USPSTF also recommends screening all adults for hypertension, and recommends hyperlipidemia screening in males over age 35, females over age 45 and younger individuals with additional cardiovascular disease risk factors.[75] If a subgroup of persons with diabetes or prediabetes derives benefit from antihypertensive, lipid-lowering, aspirin, glycemic control treatment, or lifestyle interventions, and these people would not have been detected by hypertension or hyperlipidemia screening, or because of hyperglycemia symptoms, then there might be a rationale for screening a larger group of individuals.

The presence of hyperlipidemia as defined by high LDL levels does not clearly identify those who would benefit from lipid-lowering treatment, as persons with high triglyceride or low HDL levels also benefit. In the HPS, persons with diabetes benefited from lipid-lowering treatment regardless of initial LDL level.[95] A large primary prevention trial using fixed-dose atorvastatin compared with placebo (the Collaborative Atorvastatin Diabetes Study [CARDS] study)[229] in persons with diabetes found significant reduction in cardiovascular events and stroke regardless of baseline LDL levels. (We excluded this study from our review given that it was not a newly-diagnosed population and there was no subgroup without diabetes to use to compare relative benefits of treatment.)

Many persons with diabetes are hypertensive and/or have additional cardiovascular disease risk factors and those with the highest cardiovascular risk profiles are likely to benefit most from treatment.[95, 99, 223, 229, 230] It is therefore likely that many people with diabetes would have qualified for diabetes screening according to current USPSTF guidelines. The prevalence of diabetes among persons with average cardiovascular risk and no history of hypertension or dyslipidemia is unclear. A general population screening study found that screening persons simply on the basis of an age over 45 years was of very low yield, and nearly three-quarters of those found to have DM2 had a history of hypertension or were hyperlipidemic.[45]

There is good evidence that persons with diabetes and hypertension benefit from aggressive blood pressure lowering.[94] There is therefore a reasonable rationale for screening hypertensive individuals for diabetes since this might alert physicians to aim for lower blood pressure targets.

There was a significant risk reduction in cardiovascular events in the diabetic group assigned to the lowest blood pressure target, and the mean achieved blood pressure in that group was 135/81 mmHg. So, in defining hypertension for the purposes of screening, one could consider 135/80 as a threshold that should prompt screening.

Prediabetes populations are heterogeneous, with variation in cardiovascular disease risk and in the pathway and ultimate progression to DM2; those with IGT likely have an elevated risk of cardiovascular disease.[25, 26, 231, 232] Lifestyle intervention can improve cardiovascular risk profiles in prediabetic individuals, but there is currently little evidence demonstrating a reduction in health outcomes.[138, 140, 233]

Older individuals with diabetes are at substantial risk for cardiovascular disease, and likely do derive some benefit from cardiovascular risk reduction, but it is not clear that the diagnosis of diabetes would significantly alter the approach to treatment in these individuals.[94, 95, 234] The role of tight glycemic control in older adults with diabetes is unclear. Given the relatively long duration of follow-up required to derive benefit from tight glycemic control and the exclusion of persons with limited life expectancy from many of the trials discussed herein, the implications of the diagnosis of diabetes in those with limited life expectancy is uncertain.

The possibility exists of a "legacy effect" of an early, aggressive glycemic control strategy in persons with diabetes whereby early initial aggressive management can produce improvements in clinical outcomes after many years of follow-up.[235] The largest study of an initial strategy of sustained tight glycemic control in type 1 diabetes[236] recently published an extension study with 17 years of follow-up accrued, and the results suggest that participants originally randomized to a tight glycemic control strategy experienced a significant reduction in cardiovascular events at long-term follow-up, despite similar glycemic control in the intervention and control groups during post-randomization follow-up.[237] However, there is, as yet no evidence confirming this in persons with DM2. The UKPDS followed persons with diabetes for an average of 10 years, but more substantial benefit in cardiovascular outcomes may require an even longer follow-up period.

In persons with prediabetes, longer-term follow-up of the Finnish Diabetes Prevention Study revealed a significant, sustained relative risk reduction in diabetes incidence of 36%.[153] It is unclear from these data whether the sustained reduction in diabetes incidence was due to maintenance of lifestyle changes in the intervention group or the "legacy effect" from the intervention period itself.

Harms of Screening

The potential yield of diabetes and prediabetes screening must be weighed carefully against the potential harms of screening and diagnosis. We did not identify evidence suggesting serious adverse effects of a new diagnosis of DM2 achieved via screening. The literature does, however, have significant limitations. Included studies examined persons at high risk of developing diabetes, and thus the results may not be applicable to mass screening programs which are not targeted.[178-180] There are other theoretic concerns with screening such as the effects of

labeling[238] and the financial and insurance ramifications of a new diagnosis, but to date there is not sufficient evidence to support or refute these concerns.

Limitations

As there is very little direct evidence on the benefits of screening interventions for DM2, we reviewed and synthesized indirect evidence: treatment interventions for persons with newly-diagnosed DM2, comparisons of treatments between persons with and without diabetes, and modeling studies. There are a number of important limitations inherent in using indirect evidence.

We restricted our review of treatment for diabetes to studies with mean diabetes duration one year or less, as we felt that these populations would most closely resemble screen-detected populations. Since the natural history of diabetes and the progression from prediabetes to asymptomatic diabetes to diagnosed disease is not completely elucidated and there may be much variability, it remains unclear whether this restriction is valid. Individuals with long-standing DM2 (and more microvascular and macrovascular disease) will likely show greater benefits from treatment. Limiting applicable evidence on DM2 treatment to early disease only will shed a less favorable light on the effectiveness of treatment (and therefore screening) interventions. For studies comparing a given treatment among persons with and without DM2, we included studies with any duration of disease, and the applicability of these data to populations with screen-detected disease is uncertain.

Attempts to divide diagnosed patients into those with a "clinical diagnosis" based on symptoms, and those deemed to be "screened" due to alleged asymptomatic status do not truly compare "screened" to "not screened" patients, limiting the conclusions that can be drawn from comparisons between these two groups. However, studies such as the in-progress ADDITION study[88] and the Hoorn study[41] do provide useful data on risk profiles and outcomes with early treatment, particularly in view of the infeasibility of a trial randomizing persons to screening or no screening and following for long-term health outcomes. Also, as discussed above, given current opportunistic screening practices targeting high-risk groups and the ubiquity of glucose measurements in lab batteries drawn for other reasons (e.g., chemistry panels), the construct of clinical diagnosis versus screening asymptomatic individuals may not reflect true current practice.

Most of the data on diabetes treatment were from prespecified subgroup analyses of large trials which included both diabetic and nondiabetic populations. As discussed above, there are clear and important differences between the diabetes and non-diabetes subgroups, and the subgroup analyses were often underpowered to demonstrate significant changes in primary outcomes. Prevention trials among persons with prediabetes were powered to examine the primary outcome of new cases of DM2, and not to examine long-term health outcomes such as cardiovascular events.

Modeling studies can provide important insights into potential benefits, harms, and costs of screening and treatment interventions at the individual or population level. Models rely on data

from observational studies and trials, and are only as good as the data and assumptions underlying them. All six models that we identified that examined the effect of screening interventions[13, 43, 87, 90-92] lack transparency to some degree, and all have had one or more of their important underlying assumptions criticized.[13]

Emerging Issues/Next Steps

The ADDITION study[88] should be available in 2010 and will provide important data on the effectiveness of treatment of screen-detected DM2 populations on long-term health outcomes.

Future Research

The progression from normoglycemia to DM2 is complex and varied. Further research is needed to define the duration of the prediabetes phase and identify measurable risk factors for progression to DM2 and its complications. The relative roles of IFG versus IGT as cardiovascular risk factors need further delineation. It may be possible to stratify persons with prediabetes based on glycemia or other characteristics (e.g., visceral fat distribution) that might be helpful in identifying subpopulations, which would benefit most from the identification of prediabetes.

Diabetes prevention studies have primarily focused on IGT, a population that is not picked up by fasting plasma glucose, the currently recommended DM2 screening test.[46] In addition, only 24% of persons with prediabetes have IFG,[239] and IGT may be more predictive of mortality.[21] Thus further research is needed to determine optimal approaches to identifying persons at high risk for cardiovascular events, given that the OGTT is infeasible as a universal screening test.

Further research examining lifestyle interventions which link sustainable improvements in insulin resistance to other cardiovascular risk factors, and improvements in pancreatic beta cell function to improvements in health outcomes in real-world settings would be useful in determining the long-term utility of screening for prediabetes, particularly in view of the low risk of adverse effects from lifestyle interventions.

The cost-effectiveness of diabetes screening programs is considered to be mainly determined by the long-term health benefits rather than the cost of detection and treatment of diabetes.[240] Thus, long-term, sustainable interventions which impact health outcomes, and with a low risk of harms, need to continue to be the focus of intervention research. Further work is needed to examine the psychological and labeling effects of both the screening procedure and a new diagnosis of prediabetes or DM2. It is unclear what effect screening and diagnosis have on important determinants of behavior and health, such as self-efficacy and motivation for lifestyle change, intermediate outcomes, such as weight and physical activity, as well as long-term health outcomes. Persons with newly-diagnosed diabetes may adapt to their disease over time, and it is important to understand if screen-detected persons adapt over time also.

Given the burden of cardiovascular morbidity and mortality among persons with diabetes, as well as the uncertainty in assessing true cardiovascular risk among persons with diabetes, future studies might compare cardiovascular event rates among different subgroups of persons with diabetes. Screening protocols targeted to different risk factors (i.e., risk for diabetes diagnosis versus overall cardiovascular risk) should be examined and compared. Specifically, it would be useful to know if cardiovascular risk factors other than hypertension or hyperlipidemia identify persons with diabetes who might benefit from early identification and treatment.

Further modeling studies would be helpful if they examined the effect of screening targeted to persons with cardiovascular risk factors in addition to hypertension. As data become available, existing, high-quality models need to be updated and underlying assumptions reexamined. Modeling studies may also be useful to examine demographic subgroups such as racial and ethnic minorities, as well as re-screening intervals and optimal screening ages.

Conclusions

The Summary of Evidence Table (Table 11) shows summarized evidence per Key Question. There are no RCTs examining the effectiveness of a screening program for DM2. The only direct evidence is a small, case-control study, which did not suggest a benefit from screening when microvascular complications were considered.[84] The ADDITION study,[88] which is currently in progress, may shed light on the long-term health outcomes of screen-detected DM2. Modeling studies suggest that screening for DM2 may be relatively cost-effective when macrovascular benefits of optimal blood pressure control are taken into account, and older persons may benefit more than younger age groups. The available evidence suggests that there are no serious adverse effects of a new diagnosis of DM2 achieved via screening.

There is clear evidence that intensive lifestyle interventions and some pharmacotherapies can decrease the incidence or delay the onset of diabetes up to 7 years. There is, however, no direct evidence that screening for prediabetes and intervening in screened-positive persons has health benefits compared to waiting to intervene at the time of clinical diagnosis. Several recent studies report cardiovascular outcomes, but these studies were either not powered to examine these outcomes, or they had other methodological limitations.

Cardiovascular events are the most frequent cause of morbidity and mortality in persons with diabetes; and elevated risk for cardiovascular events may occur early on, extending into the prediabetic period. It is not clear to what degree diabetes reflects atherogenic risk in persons with few other traditional risk factors. It is also not clear how to approach individuals with only borderline traditional risk factors, e.g., borderline hypertension or mildly elevated LDL levels (such as 120 mg/dl), and whether diabetes substantially elevates cardiovascular risk in these individuals. It is likely that there are diabetes subgroups that have a propensity towards atherosclerosis, while others have a more benign form of the disease. Future research should investigate screening algorithms incorporating such information that may identify and target more aggressive follow-up and treatment for those persons with DM2 with the highest cardiovascular risk.

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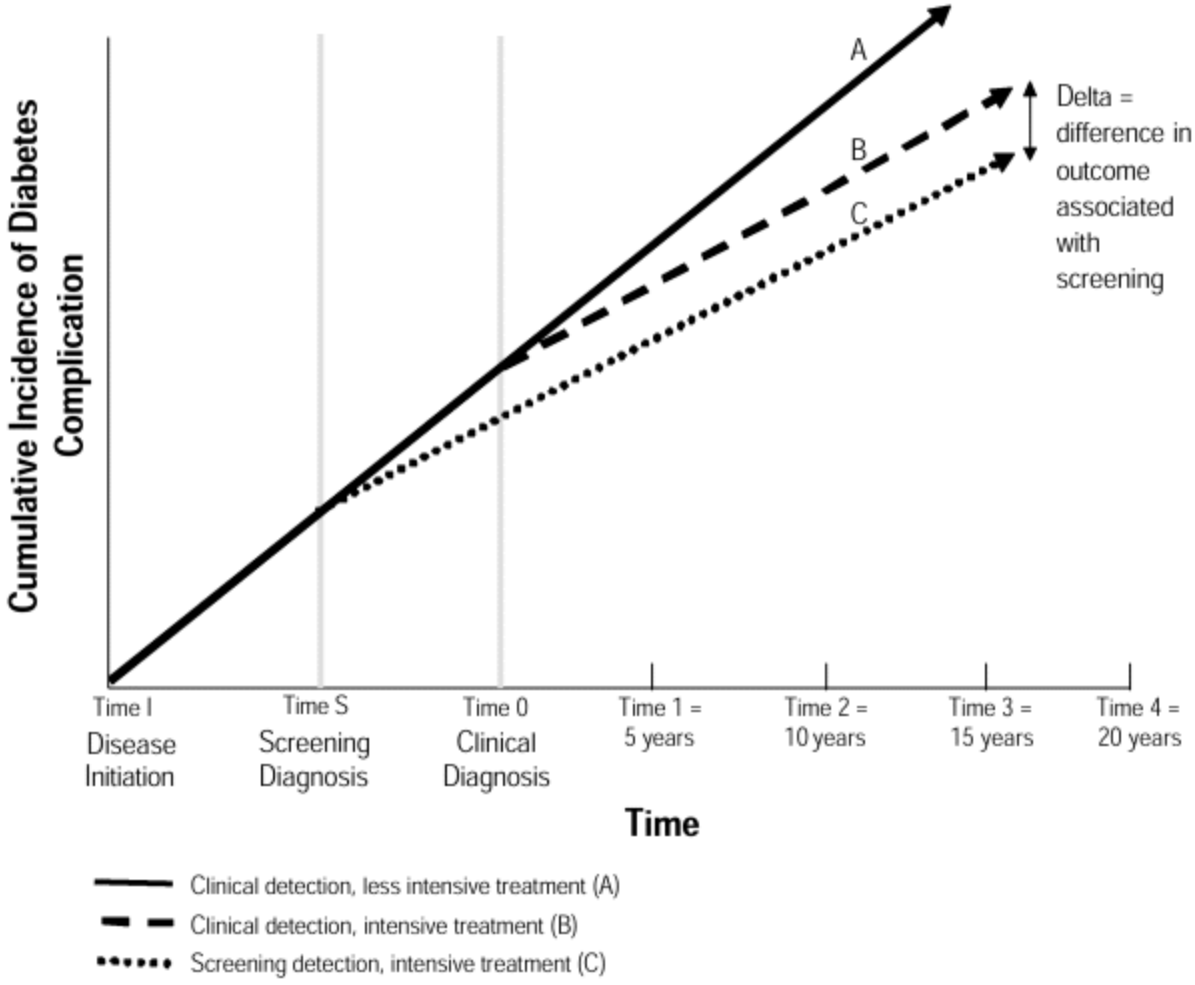
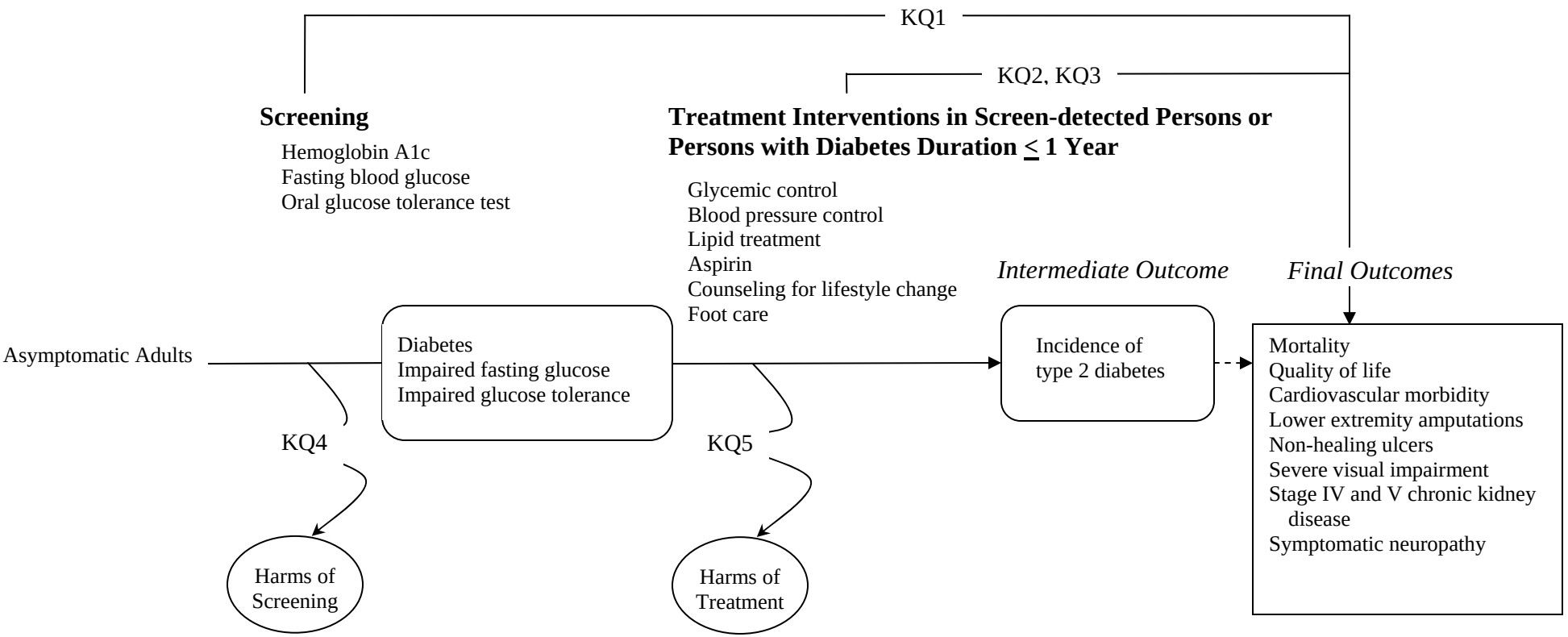
Figures

FIGURE 1. THE "DELTA QUESTION" IN SCREENING FOR TYPE 2 DIABETES*



*Reprinted from Harris RP, Lux LJ, Bunton AJ, Sutton SF, Lohr KN, Donahue KP, et al. Screening for Type 2 Diabetes Mellitus. (Prepared by RTI International Evidence-based Practice Center under contract 290-97-0011 for the Agency for Healthcare Research and Quality.) Rockville, MD: U.S. Department of Health and Human Services; February 2003. Systematic Evidence Review no. 19.

FIGURE 2. ANALYTIC FRAMEWORK AND KEY QUESTIONS



KQ 1. Is there direct evidence that systematic screening for type 2 diabetes, IFG, or IGT among asymptomatic adults over the age of 20 years at high-risk for diabetes complications improves health outcomes? Does it improve health outcomes for asymptomatic individuals at average-risk for diabetes complications?

KQ 2. Does beginning treatment of type 2 diabetes in adults early as a result of screening provide an incremental benefit in health outcomes compared with initiating treatment after clinical diagnosis?

KQ 3. Does beginning treatment for IFG and/or IGT in adults early as a result of screening provide an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis of type 2 diabetes?

KQ 4. What adverse effects result from screening an adult for type 2 diabetes or IFG/IGT?

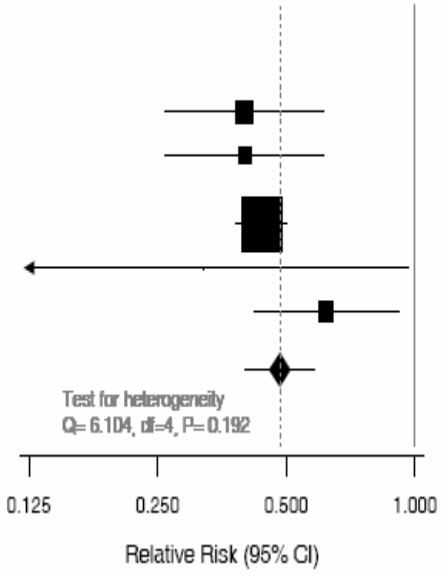
KQ 5. What adverse effects result from treating an adult with type 2 diabetes, IFG, or IGT detected by screening?

Abbreviation: KQ: key question.

FIGURE 3. DIABETES INCIDENCE

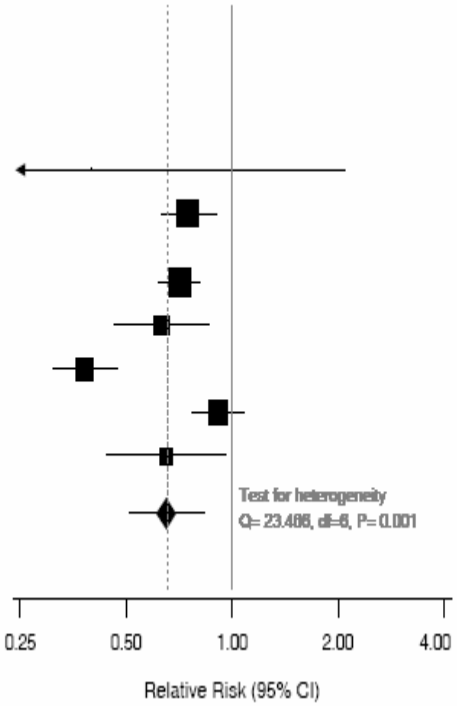
Lifestyle Trials

	Follow-up* (Yrs)	Number of subjects Control group	Intervention group	RR (95% CI)
Pan, 1997	6	133	397	0.60 (0.43, 0.83)
Tuomilehto, 2001	3.2	257	265	0.40 (0.26, 0.61)
Diabetes Prevention Program Research Group, 2002	2.8	1082	1079	0.44 (0.38, 0.50)
Kosaka, 2005	4	356	102	0.32 (0.11, 0.96)
Ramachandran, 2006	3	136	133	0.62 (0.42, 0.92)
All studies combined				**0.48 (0.40, 0.58)**



Drug Trials

	Drug	Follow-up* (Yrs)	Number of subjects Control group	Intervention group	RR (95% CI)
Heymsfield, 2000	Orlistat	2	53	67	0.40 (0.08, 2.08)
Chiasson, 2002	Acarbose	3.3	715	714	0.75 (0.63, 0.90)
Diabetes Prevention Program Research Group, 2002	Metformin	2.8	1082	1073	0.71 (0.62, 0.81)
Torgerson, 2004	Orlistat	4	1637	1640	0.63 (0.46, 0.86)
DREAM Trial Investigators, 2006	Rosiglitazone	3	2635	2634	0.38 (0.31, 0.47)
DREAM Trial Investigators, 2006	Ramipril	3	2646	2623	0.91 (0.77, 1.08)
Ramachandran, 2006	Metformin	3	136	133	0.65 (0.44, 0.96)
All studies combined					**0.65 (0.51, 0.83)**



*Mean or median follow-up time

Summary Tables

TABLE 1. DIABETES GUIDELINES

Organization *Year*	Screening Test	Recommendations
American Academy of Family Physicians[71] *2003*	FPG test or 2-h OGTT (75-g glucose load); the recommended initial screening test in nonpregnant adults is FPG.	Follows 2003 recommendations of US Preventive Services Task Force.
American Diabetes Association[46] *2007*	FPG test or 2-h OGTT (75-g glucose load); the recommended initial screening test in nonpregnant adults is FPG	Testing should be considered in all adults at age 45 years and above, particularly those with BMI ≥ 25 (kg/m^2); if normal, repeat at 3 year intervals. Testing should be considered in younger adults or carried out more frequently if BMI ≥ 25 (kg/m^2) and have additional risk factors (physically inactive, family history of diabetes, high-risk ethnic population, hypertension, prediabetes, have vascular disease, HDL <35 mg/dl and/or triglyceride >250 mg/dl Screen for pre-diabetes and diabetes in high-risk, asymptomatic, undiagnosed adults and children in health care setting.
Australian evidence-based guideline[72] *2001*	FPG should be measured for initial screening; OGTT for all people with an equivocal result	Recommend identifying and treating type 2 diabetes at a stage before clinical presentation; case detection has a favorable risk:benefit ratio; screening and diagnostic tests are cost-effective and safe; potential harms are uncertain. High risk individuals (IGT, IFG, > 45 years with hypertension or BMI > 30, known cardiovascular disease, women with polycystic ovary syndrome who are obese, various ethnic groups) Recommend testing each year for people with IGT or IFG and every 3 years for people with high risk and a negative screening test.
Diabetes UK[73] *2006*	Limited evidence available to identify the most effective and practical method of screening. Recommends fasting capillary or venous blood glucose measurement Test every 3 years for those with increased risk.	General population screening is not recommended. Targeted case finding of high risk groups is encouraged (Caucasians >40 years and minority ethnic groups > 25 years with one or more risk factors [family history, overweight or obese, sedentary]; people with known IFG or IGT; women who have had gestational diabetes; women with polycystic ovary syndrome who have a BMI > 30; people who have ischemic heart disease, cerebrovascular disease, peripheral vascular disease or treated hypertension)
US Preventive Services Task Force[75] *2003*	FPG test or 2-h OGTT (75-g glucose load); the recommended initial screening test in nonpregnant adults is FPG.	The evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose. Could not determine the balance of benefits and harms of routine screening. Recommends screening for type 2 diabetes in adults with hypertension or hyperlipidemia.
World Health Organization[74] *2003*	Method(s) should depend on resources available, acceptability of method for the population, and levels of sensitivity and specificity required	There is no direct evidence (i.e., from randomized controlled trials) that individuals will benefit from early detection of type 2 diabetes through screening. Health authorities and professional organizations should formulate their own policies based on individual benefits and costs.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

TABLE 2. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author Year (in date order)	Type of screening; Perspective	Type of model; Time horizon	Population Country	Included costs; Discount rate	Intervention	Outcomes	Conclusions	Quality assessment
CDC Diabetes Cost-Effectiveness Study Group 1998[90]	One-time opportunistic screening during regular physician visit; Single-payer health care system	Monte Carlo computer simulation model Lifetime or age 95y	10,000 cohort with newly-diagnosed DM2; general population US	Used data from DM1 for microvascular disease risk reduction with treatment 3% annual rate	One-time screening intervention with FPG, OGTT for confirmation of positives	Incremental cost of screening is $236,449 per life-year gained and $56,649/QALY; more CE among younger persons and among African Americans	Screening may produce cost/QALY within range of currently acceptable, especially for younger persons Model does not take into account effect of blood glucose control on CVD	Limited sensitivity analyses CVD not modeled; screening and treatment only influence microvascular complications No information on how QALYs determined No mention harms of screening Lack of transparency of details of model Used data from DM1 for microvascular disease risk reduction with treatment
Goyder et al, 2000[91]	Universal screening Perspective: NA (does not involve cost)	Decision analysis Lifetime	10,000 cohort UK	NA 3% annual rate for QALYs	Various interventions for hyperglycemia, HT, lipids	QALYs gained by screening 10,000 persons: 10.5	The immediate disutility of earlier diagnosis and additional treatment may be greater than the potential long-term benefit from postponing microvascular complications; screening decisions should be based largely on CVD risk and interventions to reduce that risk	Used data from DM1 for microvascular disease risk reduction with treatment Details and assumptions of the model not clear
Hofer et al, 2000[92]	Mass screening Not an economic analysis	Markov model Lifetime	Recent onset of diabetes (<5y) derived from NHANES III	NA	Hypertension and lipid NHANES III; DCCT	Number blind/1000 diabetics age 40y, A1c 12%: Case finding: 141 Perfect screening: 133 Case finding, A1c <9%: 90 Screening, A1c <9%: 41 Screening produces 7% of the benefit of reduced number of cases of blindness; improved treatment alone is 65%	Largest impact of improving treatment and diagnosis is in younger persons with high A1c; focus should first be on improving glycemic control of known diabetics with high A1c; if that is achieved, then the benefits of screening will become more important	Does not include benefits of HT and lipid treatment Only examines microvascular complications

TABLE 2. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author Year (in date order)	Type of screening; Perspective	Type of model; Time horizon	Population Country	Included costs; Discount rate	Intervention	Outcomes	Conclusions	Quality assessment
Chen et al, 2001[43]	Mass screening Single payer health plan	Markov process Monte Carlo simulation 30y or death	Over age 30y, general community population Taiwan	Direct costs including costs of screening, treatment 3% annual rate	Screening program lasts for 10y; standard treatments such as that of UKPDS for persons with DM2	Cumulative incidence rates of microvascular complications with screening: 2y frequency: Blindness: 3.06%; ESRD: 0.19%; LEA: 0.97% 5y frequency: Blindness 3.13%; ESRD: 0.19%; LEA: 0.99% Control (no screening): Blindness: 4.3%; ESRD: 0.54%; LEA: 1.43% NSD between 2 and 5y screening CE (cost/QALY): 2y: $17,833; 5y: $10,531 Incremental cost/QALY: lowest 40-49y group ($9,193), highest 70+y ($36,467)	Mass screening is relatively cost-effective compared to opportunistic screening as costs incurred with mass screening are offset with life-years gained Mass screening for DM2 is relatively cost-effective compared to other screening interventions (e.g., cervical cancer or HT) Screening is more cost-effective in younger than older persons Model focuses on microvascular complications	Lack of transparency for assumptions, data synthesis No sensitivity analyses Does not include CVD risk reduction in model Does not include adverse effects of screening
Hoerger et al, 2004[87]	One-time opportunistic screening targeted to persons with HT Health care system perspective	Markov Lifetime	General primary care population US	Direct medical costs: screening, diagnostic tests, treatment 3% annual rate	Treatment of HT to goal of DBP 80mm Hg (HOT); intensive glycemic control for diagnosed DM2 (UKPDS)	Results per true diabetes case, compared to no screening: QALYs gained per person screened (cost/QALY): Targeted screening for people with HT only: range 0.08 with screening at 35y ($87,096) to 0.23 for screening at 65y ($31,228) Universal screening: range 0.05 with screening at 35y ($126,238) to 0.11 for screening at 75y ($48,146) Universal vs targeted screening, incremental cost/QALY: 35y: $143,830; 75y $443,433	Targeting screening to persons with HT is more CE than universal screening at every age when each alternative is compared to no screening Targeted and universal screening more CE when take into account reduction in CVD events from earlier treatment of HT for ages 55, 65, 75 than for 35 and 45y The most CE approach to one-time screening: target people with HT 55 to 75y Benefit of screening comes mainly from reducing CVD events by control of HT rather than from reducing microvascular complications	Did not include adverse effects of screening Thorough sensitivity analyses Includes sub-models for CVD and stroke Includes benefits for tight BP control, but not other CVD risk reduction interventions Assumes 100% uptake and follow-up

TABLE 2. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author Year (in date order)	Type of screening; Perspective	Type of model; Time horizon	Population Country	Included costs; Discount rate	Intervention	Outcomes	Conclusions	Quality assessment
Glumer et al, 2006[93]	Population screening Health care system	Population-based simulation model 5y	Community-based Denmark	Screening and treatment for DM2 and complications	Based on community sample age 30-60y	Least conservative model (low costs and multiplicative risk reduction for combined treatments): Cost/number of events prevented: £23,000 to 82,000; major contributors to uncertainty: risk reduction for hypertension treatment and UKPDS risk model intercept Model not sensitive to decisions about which groups to screen nor to costs of screening or treatment; model strongly affected by assumptions about how treatments combine to reduce risk.	There is considerable uncertainty about the CE of screening for DM2; the most important parameter is the effect of treatment and whether risk reductions are multiplicative or additive	Model combines effects of treatment of hyperglycemia, hypertension and dyslipidemia Time horizon only 5y
Waugh et al, 2007[13]	Population screening National Health Service	Markov Lifetime	General population UK	Screening and treatment for DM2 and complications 3.5% for costs and benefits	Screen with A1c then OGTT Various interventions for hyperglycemia, HT, lipids	Cost reduction and QALYs gained from fewer CVD events, largely from statin treatment, as well as fewer microvascular complications	Screening is relatively cost-effective for persons 40-70y; more CE for the older group and for persons with hypertension or obesity	Includes macro and microvascular complications; relatively simple model

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DCCT, Diabetes Control and Complications Trial; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; CDC, Centers for Disease Control and Prevention; CE, cost-effectiveness; ESRD, end-stage renal disease; FPG, fasting plasma glucose; HOT, Hypertension Outcomes Trial; HT, hypertension; LEA, lower extremity amputations; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; NSD, no significant difference; OGTT, oral glucose tolerance test; QALYs, quality adjusted life-years; UK, United Kingdom; UKPDS, United Kingdom Prospective Diabetes Study; y, year(s).

TABLE 3. RANDOMIZED CONTROLLED TRIALS OF HYPERTENSION TREATMENT IN DIABETIC POPULATIONS (KQ2)

Study Author, year	Intervention	Sample size (diabetes subgroup/ total)	Baseline cardiovascular risk factors*	Achieved blood pressure (mm Hg)	Outcomes	*Quality rating*; comments
ALLHAT (*Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial*) Whelton et al, 2005[103] ALLHAT Officers, 2002[115] Barzilay et al, 2001[231]	Chlorthalidone vs lisinopril vs amlodipine†	13,101 / 31,512	HTN: 100/100 History of CVD: 36% / 62% Smoking: 13% / 28% Hyperlipidemia: NR	Mean SBP (SD) in DM subgroup: Chlorthalidone: 135.0 (15.6) Amlodipine: 136.3 (15.9) ‡ Lisinopril: 137.9 (19.0) ‡ Mean SBP (SD) in normoglycemia subgroup: Chlorthalidone: 133.4 (14.9) Amlodipine: 133.5 (14.1) Lisinopril: 134.8 (17.3)	Fatal CVD or nonfatal MI in the DM subgroup: Amlodipine-chlorthalidone: 0.97 (0.86 - 1.10), p = 0.64 Lisinopril-chlorthalidone: 0.97 (0.85 - 1.10), p = 0.59 Fatal CVD or nonfatal MI in the normoglycemia subgroup: Amlodipine-chlorthalidone: 0.94 (0.82 - 1.07), p = 0.36 Lisinopril-chlorthalidone: 1.02 (0.89 - 1.16), p = 0.79 Difference between DM and normoglycemia subgroups: p = NR§	*Fair*; significantly higher rate of attrition in the lisinopril group
CONVINCE (*Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial*) Black et al, 2003[104]	Verapamil vs atenolol or HCTZ	3,239 / 16,476	HTN: 100% Hyperlipidemia: 31.2% Previous MI: 7.6% Established vascular disease: 16.7% Stroke: 4.6%	Mean SPB/DBP in total study sample (DM subgroup NR): Verapamil: 136.5 / 79.0 Atenolol or HCTZ: 136.6 / 79.5	Fatal CVD, stroke, or MI: DM subgroup: 0.86 (0.66 - 1.12), p = NR Normoglycemia subgroup: 1.10 (0.92 - 1.31), p = NR Difference between DM and normoglycemia subgroups: p = 0.16§	*Fair*

* Data reported as percentages for the DM/non-DM groups in the ALLHAT study and for the total study sample for the CONVINCE study (data for the DM subgroup alone NR)
† Doxazosin arm was prematurely discontinued because of an excess of heart failure events
‡ $p < 0.5$ compared with chlorthalidone
§ p-value for interaction between diabetes and normoglycemia subgroups for primary outcome

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes; HCTZ, hydrochlorothiazide; HR, hazard ratio; HTN, hypertension; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; MI, myocardial infarction; NR, not reported; RR relative risk; SBP systolic blood pressure.

TABLE 4. RANDOMIZED CONTROLLED TRIALS OF LIPID INTERVENTIONS IN DIABETIC AND NONDIABETIC POPULATIONS (KQ2)

Study Author, Year	Intervention	Sample Size (Diabetes Subgroup/ Total), *n/n*	Baseline Cardiovascular Risk Factors	Mean Achieved LDL-C Level (SD), *mg/dL*	Outcome: Relative Risk (95%CI)	*Quality*; Comments
ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*) Allhat Officers, 2002[115]	Pravastatin titrated to achieve 25% reduction in LDL-C vs. usual care	3635/ 10 355*	Total group (DM subgroup information NR): HTN: 100% History of CVD: 14.2% Smoking: 23.1% Mean LDL-C: 145.6 mg/dL (SD, 21.4)	Pravastatin: 104.0 (29.1) Usual care: 121.2 (34.6)	All-cause mortality, pravastatin vs. usual care†: DM subgroup: 1.03 (0.86–1.22); *P* = NR Non-DM subgroup: 0.96 (0.84–1.1); *P* = NR CHD death or nonfatal MI: DM subgroup: 0.89 (0.71–1.10); *P* = NR Non-DM: 0.92 (0.76–1.10); *P* = NR Difference between diabetes and normoglycemia subgroups‡: *P* = NR	*Fair*; Relatively small difference in LDL-C between intervention and usual care groups due to withdrawals in intervention group and off-protocol statin use in usual care group
ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial*) Sever et al, 2003,[116] 2005[118]	Atorvastatin, 10 mg, vs. placebo	2532/ 10 305	DM/total group: HTN: 100%/100% Mean LDL-C: 28.7 mg/dL (SD, 27.3)/124.8 mg/dL (SD, 27.3) Smoking: 20.3%/32.2% Cerebrovascular disease: 7.5%/9.7% Peripheral vascular disease: 5.3%/5.0% Mean number CVD risk factors: 4.1/3.7	Atorvastatin: 83.9 (26.5) Placebo: 117.8 (30.4)	Nonfatal MI or fatal CHD†: DM subgroup: 0.84 (0.55–1.29); *P* = NR Non-DM subgroup: 0.56 (0.41–0.77); *P* = NR Total CVD events and procedures: DM subgroup: 0.77 (0.61–0.98); *P* = NR Non-DM subgroup: 0.80 (0.68–0.94); *P* = NR Difference between diabetes and normoglycemia subgroups‡: *P* = 0.82	*Fair*; Study stopped early; relatively low number total events in diabetes subgroup
HPS (Heart Protection Study) HPS, 2003[95]	Simvastatin, 40 mg, vs. placebo	5963/ 20 536	DM/non-DM: Previous MI: 19%/51% Other history of CVD: 14%/28% Smoking: 67%/78% Blood pressure: 148/82 mm Hg/143/81 mm Hg Mean LDL-C: 124.8 mg/dL (SD, 32.0)/132.6 mg/dL (SD, 32.0)	Simvastatin: 89.7 Placebo: 128.7	Nonfatal MI or fatal CVD†: DM subgroup: 0.73 (0.62–0.85); *P* < 0.001 Non-DM subgroup: 0.73 (0.66–0.81); *P* < 0.001 Stroke: DM subgroup: 0.76 (0.61–0.94); *P* = 0.01 Non-DM subgroup: 0.74 (0.64–0.86); *P* < 0.001 Difference between diabetes and normoglycemia subgroups‡: *P* = 0.10	*Good (for overall trial)*; Baseline characteristics differed significantly between diabetes and normoglycemic subgroups

TABLE 4. RANDOMIZED CONTROLLED TRIALS OF LIPID INTERVENTIONS IN DIABETIC AND NONDIABETIC POPULATIONS (KQ2)

Study Author, Year	Intervention	Sample Size (Diabetes Subgroup/ Total), *n/n*	Baseline Cardiovascular Risk Factors	Mean Achieved LDL-C Level (SD), *mg/dL*	Outcome: Relative Risk (95%CI)	*Quality*; Comments
PROSPER (*Prospective Study of Pravastatin in the Elderly at Risk Trial*) Shepherd et al, 2002[117]	Pravastatin, 40 mg, vs. placebo	623/ 5804	Total group (DM subgroup information NR): Previous angina: 26.9% Previous MI: 13.4% Cerebrovascular disease: 11.2% Vascular disease: 44.2% Mean LDL-C: 148.2 mg/dL (SD, 31.2) Hypertension: 61.9% Smoking: 26.8%	Mean LDL at 3 months: Pravastatin: 96.7 Placebo: 146.6	Nonfatal MI, fatal CVD, nonfatal and fatal stroke†: DM subgroup: 1.27 (0.90–1.80); *P* = NR Non-DM subgroup: 0.79 (0.69–0.91); *P* = NR Difference between diabetes and normoglycemia subgroups‡: *P* = 0.015	*Fair*; Little diabetes-specific information and relatively few persons with diabetes limit conclusions

* Including persons in the doxazosin group
† Primary outcome
‡ *P* value for interaction between DM and normoglycemia subgroups for primary outcome

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported.

TABLE 5. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES (KQ2)

Author, Year Model (in date order)	Type of screening; Perspective	Type of model Time Horizon	Population Country	Included costs Discount rate	Intervention Data sources	Outcomes	Conclusions
Global Diabetes Model Brown et al, 2000[126, 133]	NA Payer	Monte Carlo microsimulation, using continuous prediction equations 20y	5000 newly diagnosed DM2 white males; no CVD or other macro- or microvascular complications; based on Kaiser health maintenance organization US	Direct medical costs 0%	Intensive lipid management (LDL from 150 to 100 mg/dl and HDL from 40 to 50 mg/dl) Kaiser databases, world scientific literature, observational data such as Framingham Heart Study	A1c 9.5%, SBP 130: % survival: 82.7% Total costs per person ($US): $85,920 Lower costs for lower A1c, higher costs for higher SBP	Survival improves with intensive lipid therapy
CDC/RTI (*Center for Disease Control and Prevention/ Research Triangle Institiute*) Diabetes Group 2002[123]	Health care system (for costs)	Markov model; emphasis on macrovascular complications Subjects proceed through 5 different disease paths; nethropathy, neuropathy, retinopathy, CVD, stroke Death or age 95y	Newly diagnosed DM2; 55% female, 8% 25-34y, 8% 35-44y, 26% 45-54y, 18% 55-64y, 23% 65-74y, 13% 75-84, 4% 84-94y US	Health care system only; no indirect or direct patient costs Costs and QALYs discounted at 3% annually	All subjects received conventional treatment to control BG (UKPDS control arm) Intensive glycemic control: to reduce FPG to <108 mg/dl using chlorpropamide, glipizide, insulin Intensified HT control: ACE-I or Beta-blocker for baseline BP≥160/95 Reduction in TC: pravastatin for baseline level ≥200 mg/dl UKPDS and other sources	Intensive glycemic control applied to all persons newly diagnosed with DM2 in the US: increase in QALY of 0.1915 (discounted), CE ratio: $41,384 per QALY; CE ratio increases markedly with age; cumulate incidence of nethropathy, neuropathy, retinopathy decreased by 11 to 27% Intensified HT control: increased QALYs by 0.392 relative to moderate HT control; CE ratio - $1,959/QALY (ie cost savings); age had little effect; Reduction in TC: increase discounted QALYs 0.3475, CE ratio $51,889 per QALY, lowest ratio for 45-85y	Intensified HT control reduced costs and improved health outcomes relative to moderate HT control; intensive glycemic control and reduction in serum TC increase costs and improve health outcomes Intensive glycemic control is most cost-effective for younger persons

TABLE 5. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES (KQ2)

Author, Year Model (in date order)	Type of screening; Perspective	Type of model Time Horizon	Population Country	Included costs Discount rate	Intervention Data sources	Outcomes	Conclusions
CORE Model (*Center for Outcomes Research*) Palmer et al, 2004[124, 128]	Third party payer	Markov using Monte Carlo simulation; 15 submodels each of which simulates different complications associated with DM Lifetime	Newly diagnosed patients: baseline age 52y, A1c 9.1%, SBP 137 mm Hg, TC 212 mg/dl, HDL 39 mg/dl Switzerland; modeled using US payer costs	Direct medical costs; day-to-day DM management costs excluded; expressed in 2003 values in the US setting 3% annual rate for costs; outcomes not discounted	Hypothetical interventions that led to individual 10% improvements in A1c, SBP, TC, HDL UKPDS, Framingham, other published sources	QALE: increased 1.72y with improvements in all of A1c, SBP, TC, HDL Lifetime costs of DM-related complications: decreased $14,533 with improvements in all of A1c, SBP, TC, HDL; improved A1c alone: decreased $10,800, SBP alone: decreased $7,048	10% improvements in A1c, SBP, TC, HDL, individually and in combination are likely to improve length and quality of life; most marked improvement with all 4; individually A1c had greatest gains in QALE
UKPDS (*United Kingdom Prospective Diabetes Study*) Outcomes Model Clarke et al, 2005[125] 2004[131] 2003[130] 2001[129]	Health care purchaser	Probabilistic discrete-time illness-death model Lifetime (Clarke 2005[125]) Within-trial data: mean duration 10.3y (Clarke 2003[130])	Newly diagnosed DM2 aged 25-65y; mean age 52.4y, 58% male; 81% Caucasian; n=3867 UK	Direct medical costs 3.5% annually	Intensive BG control with insulin or sulphonylurea vs conventional glucose control (mainly diet); 342 patients >120% ideal body weight assigned to metformin and 411 overweight patients on conventional treatment Embedded study randomized 1148 patients with HT to BP<180/<105 vs n=758 with BP goal <150/85 mm Hg UKPDS for both outcomes and costs	QALY per patient modeled over lifetime: Intensive BG control: 0.15(-0.20, 0.49) Metformin therapy: 0.55(-0.10, 1.20) Tight BP control: 0.29(-0.14, 0.59) Probability of being cost-effective at a ceiling ratio of 20,000 Pounds per QALY: Intensive BG control: 74% Metformin therapy: 98% Tight BP control: 86% Life years gained per patient with metformin treatment versus conventional, within-trial data: 0.6 (95% CI, 0.0, 1.2)	Intensive BG control and BP control for persons with HT adds QALYs over lifetime; relatively cost-effective compared to many other accepted uses of health care resources

Abbreviations: ACE, angiotension-converting enzyme; BG, blood glucose; BP, blood pressure; CDC, Centers for Disease Control; CE, cost effectiveness; CVD, coronary vascular disease; DM2, type 2 diabetes; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; NA, Not applicable; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life years; RTI, Research Triangle Institute; SBP, systolic blood pressure; TC, total cholesterol; UKPDS, United Kingdom Prospective Diabetes Study; y, year.

TABLE 6. RANDOMIZED CONTROLLED TRIALS OF INTERVENTIONS IN PREDIABETES (KQ3)

Study Author, Year *Quality Rating*	Country	Total sample size, *n*	Mean length of follow-up	Sample characteristics*	Intervention	Outcomes
Diabetes Prevention Program DPP Research Group 2000[139] 2002[79] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	United States	3,234	2.8 y; 3.2 y for CVD outcomes	Age, 51 y (10.7); 32.3% men	Intensive lifestyle vs. metformin vs. placebo	Cumulative incidence T2DM: metformin, 58% lower (95% CI, 48%–66%); lifestyle, 31% lower (CI, 17%–43%) than placebo Cumulative incidence of CVD and CVD event rate: NSD among groups, but underpowered for this outcome
DREAM Trial DREAM Trial Investigators 2006[82, 148] 2004[147] *Good*	International multi-center	5,269	Median, 3.0 y	Age, 5.7 y (10.9); 40.8% men; BMI, 30.9 kg/m^2 (5.6)	Rosiglitazone vs. placebo; ramipril vs. placebo	Rosiglitazone: Death: HR, 0.91 (CI, 0.55–1.49); *P* = 0.7 T2DM incidence: HR, 0.38 (CI, 0.33– 0.44); *P* < 0.001 Composite CVD outcome: HR, 0.40 (CI, 0.35–0.46); *P* = 0.08 Ramipril: Death: HR, 0.98 (CI, 0.60–1.60) T2DM incidence: HR, 0.91 (CI, 0.80– 1.03) Composite CVD outcome: HR, 0.91 (CI, 0.81–1.03); *P* = 0.68
Finnish Diabetes Prevention Study Tuomilehto et al, 2001[138] Lindstrom et al, 2003[149, 150] Lindstrom et al, 2006[153] Laaksonen et al, 2005[152] Eriksson et al, 1999[151] *Fair*	Finland	522	3.2 y for post-intervention outcomes; median total follow-up, 7 y	Age, 55 y (7); 32.9% men	Lifestyle vs. usual care	Cumulative incidence of T2DM: At 3.2 y: HR, 0.4 (CI, 0.3–0.7); *P* < 0.001 At 7 y: HR, 0.57 (CI, 0.43–0.76); *P* < 0.001

TABLE 6. RANDOMIZED CONTROLLED TRIALS OF INTERVENTIONS IN PREDIABETES (KQ3)

Study Author, Year *Quality Rating*	Country	Total sample size, *n*	Mean length of follow-up	Sample characteristics*	Intervention	Outcomes
Heymsfield et al, 2000[80] *Fair-poor*	International multi-center	675	2.0 y	Age, 43.9 y; 17.5% men	Orlistat vs. placebo; both received lifestyle intervention	IGT at baseline, and at follow-up: Normoglycemia: orlistat, 71.6%; placebo, 49.1% IGT: orlistat, 25.4%; placebo, 43.4% T2DM: orlistat, 3.0%; placebo, 7.6% *P* = 0.04 between groups
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	India	531	Median, 2.5 y	Age, 54.9 y (5.7); 79.0% men	Lifestyle and metformin vs. lifestyle vs. metformin vs. placebo	Relative risk reduction in incidence of T2DM at year 3: Lifestyle: 28.5% (CI, 20.5%–37.3%) Metformin: 26.4% (CI, 19.1%–35.1%) Lifestyle and metformin: 28.2% (CI, 20.3%–37.0%)
Kosaka et al, 2005[81] *Fair*	Japan	458	4.0 y	Age, NR; 100% men	Lifestyle vs. usual care	Cumulative incidence T2DM over 4 y: lifestyle, 3%; control, 9.3%; *P* = 0.043 between groups
Pan et al, 2003[156] *Fair*	China	261	16 wk	Age, 54.5 y (8.5); 40.0% men	Acarbose vs. placebo	T2DM incidence: acarbose, 5.6%; placebo, 9.5%; *P* = 0.245

TABLE 6. RANDOMIZED CONTROLLED TRIALS OF INTERVENTIONS IN PREDIABETES (KQ3)

Study Author, Year *Quality Rating*	Country	Total sample size, *n*	Mean length of follow-up	Sample characteristics*	Intervention	Outcomes
STOP-NIDDM (*Study to Prevent Noninsulin-dependent Diabetes Mellitus Trial*) Chiasson et al, 2002[136] Chiasson et al, 2003[159] Chiasson et al, 1998[158] *Fair*	International multi-center	1,429	3.3 y	Age, 54.5 y (7.9); 49% men	Acarbose vs. placebo; both received lifestyle intervention	Cumulative incidence of: T2DM: HR, 0.75 (CI, 0.63–0.90); *P* = 0.0015 Any CVD event: HR, 0.51 (CI, 0.28–0.95); *P* = 0.02 MI: HR, 0.09 (CI, 0.01–0.72); *P* = 0.02
Swinburn et al, 2001[157] *Fair-poor*	New Zealand	136	5.0 y	Age, 52.2 y (6.5); 50.7% men	Reduced-fat diet vs. usual diet	Intervention was associated with a lower proportion of subjects with T2DM or IGT at 1 y (*P*< 0.05); NSD at 2, 3, or 5 y Included population all had IGT at recruitment, but only 31% had prediabetes with repeated testing at randomization; results are for all included patients
Watanabe et al, 2003[155] *Fair*	Japan	173	1.0 y	Age, 55.1 y (7.1); 100% men	Dietary counseling vs. usual care	T2DM incidence: NSD between groups (data not provided)
XENDOS (*XENical in the Prevention of Diabetes in Obese Subjects Study*) Torgerson et al, 2004[161] Torgerson et al, 2001[160] *Fair-poor*	Sweden	3,305 total (694 with IGT)	4.0 y	Age, 43.8 y (8.0); 44.8% men; BMI, 37.3 kg/m^2 (4.3)	Orlistat vs. placebo; both received lifestyle intervention	Cumulative incidence of T2DM in IGT subgroup after 4 y: HR, 0.551; *P* = 0.0024

* Data are means (SDs), unless otherwise noted

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; HR, hazard ratio; IGT, impaired glucose tolerance; MI, myocardial infarction; NR, not reported; NSD, no significant difference.

TABLE 7. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Perspective	Type of model Time horizon	Population Country	Included costs Discount rate	Data sources	Intervention	Outcomes	Conclusions
Segal et al, 1998[173]	Health care system	Markov 25y	Based on Australian cohort; IGT, normoglycemia and DM2	Program costs and direct medical costs 5%/y for benefits and costs	Various trial and observational data with follow-up >5y	1. Intensive weight loss and fitness program for obese 2. Standard care	Net cost per life-year saved for persons with IGT (US$): Behavioral program for seriously obese: net saving Surgery for BMI >40: $3300	Primary prevention of DM2 for persons with IGT is relatively cost-effective
Caro et al, 2004[174]	Health care system	Markov 10y or death	Representative cohort of 1000 Canadians with IGT	Direct medical costs 5%/y cost and health outcomes	Various epidemiological data sources; STOP-NIDDM; DPP; Ontario cost data	1. Acarbose 2. Metformin 3. Intensive lifestyle 4. No treatment	Incremental cost per life-year gained: relative to no treatment: Metformin: Cost savings Acarbose: Cost savings Lifestyle: $749	Treatment of IGT to prevent DM2 is cost-effective: lifestyle interventions lead to greatest healthy benefits at reasonable cost

TABLE 7. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Perspective	Type of model Time horizon	Population Country	Included costs Discount rate	Data sources	Intervention	Outcomes	Conclusions
Palmer et al, 2004[176]	Health care system	Markov Lifetime	Resembled the DPP population (IGT 5.3 -7.0 mml/l): mean age 50.6y, BMI 34.0 32% from minority population	Direct medical costs 5%/y for costs and outcomes	DPP, UKPDS	1. Intensive lifestyle (DPP intervention) 2. Metformin 3. Control	Mean number of years free from diabetes: Lifestyle: 10.0 Metformin: 9.0 Control: 8.1 Incremental increase in LE if treatment effect lasted a lifetime in years, vs control: Lifestyle: 0.90 Metformin: 0.35 Lifestyle and metformin cost savings in most countries Metformin had more impact on decreasing costs in increasing LE in younger and more obese patients	DPP produces clinically important improvements in LE, with either overall cost savings or minor increases in total costs per patient.
Archimedes Eddy et al, 2005[169] 2003[170, 171]	Patient, health plan, societal	Archimedes model built from underlying anatomy, biological variables, and pathways 5 to 30y (for societal)	Adults at high risk for DM2 (BMI >24 kg/m2, FPG 95-125 mg/dl, or 2-h OGTT 140-199 mg/dl); 100,000 simulated persons for health plan US	Direct and indirect (for societal perspective) 3%/y	Data derived from variety of empirical sources; no data are assumed; costs from DPP study, Kaiser Permanente, and others	1. DPP lifestyle program 2. Baseline: no lifestyle or other intervention 3. Lifestyle when FPG>125 mg/dl 4. Metformin as in DPP study	Individual at high-risk for DM2, 30y probability of developing DM2: baseline risk 72%; lifestyle: 61%, NNT for benefit: 9; metformin 68% Societal perspective: Incremental 30y cost/QALY: DPP lifestyle for all compared to lifestyle when FPG >125mg/dl: $201,818; Lifestyle when FPG>125 mg/dl compared to no intervention: $24,523; lifestyle intervention for all high-risk compared to no intervention: $62,600/QALY Health plan perspective: 30y cost/QALY of DPP lifestyle program compared to no intervention $143,000; increases with decreased time horizon and smaller plans; over 5y: $2.7 million	The DPP program reduces the risk of developing diabetes over a lifetime but is not particularly cost-effective compared to other health interventions

TABLE 7. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Perspective	Type of model Time horizon	Population Country	Included costs Discount rate	Data sources	Intervention	Outcomes	Conclusions
CDC/RTI (*Centers for Disease Control and Prevention / Research Triangle Institute)* Herman et al, 2005[172]	Health care system and societal	Markov; modified CDC/RTI model Lifetime	DPP population: 3234 nondiabetic persons ≥ 25y with IGT and FPG 95-125 mg/dl; mean age 51y, 68% female; 45% members of racial/ethnic minority groups US	Health care system perspective: direct medical costs; societal perspective: also included direct nonmedial costs 3%/y for costs and QALYs	DPP, UKPDS	DPP lifestyle intervention: 7% or more weight loss and 150 minutes/week of activity; or metformin 850mg bid; or placebo	Delay in onset DM2: compared to placebo: lifestyle delays onset by 11y, metformin by 3y Lifetime development of DM2: 83% in placebo, 63% with lifestyle, 75% with metformin Increase in LE compared to placebo: lifestyle 0.5y, metformin 0.2y Reduction in cumulative incidence complications: Lifestyle vs placebo: blindness 39%, ESRD 38%, amputation 35%, stroke 9%, CHD 8% Metformin vs placebo: blindness 16%, ESRD 17%, amputation 16%, stroke 3%, CHD 2% Incremental cost/QALY compared to placebo: Lifestyle: $1,124; metformin: $31,286	Lifestyle interventions are relatively cost-effective compared to placebo, producing gains in survival and a decrease in microvascular and cardiovascular complications
Lindgren et al, 2007[177]	Health care system	Markov 6y	Population-based screening in Stockholm; 60y old men and women	Direct and indirect medical costs 3%/y for costs and benefits	Finnish Diabetes Study, UKPDS, Swedish cost data	Finnish lifestyle intervention	Intervention is associated with an increase in survival of 0.18y; mean QALYs gained: 0.20y; the cost-effectiveness ratio is Euros 2,363/QALY	This model predicts that the Finnish Diabetes Study lifestyle intervention targeted at persons with high risk would be cost-savings for the health case plan and cost-effective for society

Abbreviations: BID, twice daily; BMI, body mass index; CDC, Centers for Disease Control; CHD, cardiovascular heart disease; DM2, type 2 diabetes; DPP, Diabetes Prevention Program; DPS, Finnish Diabetes Prevention Study; ESRD, end-stage renal disease; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; LE, life expectancy; NNT, number needed to treat; OGTT, oral glucose tolerance test; QALY, quality-adjusted life year; RTI, Research Triangle International; STOP-NIDDM, Stop Non-Insulin-Dependent Diabetes Mellitus study; UKPDS, United Kingdom Prospective Diabetes Study; y, year.

TABLE 8. STUDIES EXAMING THE ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design; N	Study population; Participant selection method	Follow-up	Measures used (operationalized outcomes)	Main results	Conclusions
ADDITION Study Thoolen et al, 2006[188] *Not rated*	2X2 factorial cross-sectional 196	Newly diagnosed DM2 Population-based screening in Netherlands Comparison groups = DM2 diagnosis <1y vs 2-3y	0	HADS (anxiety and depression) PAID (diabetes distress) Diabetes Illness Representations questionnaire - revised for study (perceived seriousness Diabetes self-care activities measure - revised for study (self care) Independent measures created for study (self-efficacy; perceived vulnerability)	Time effects found for perceived vulnerability (increases significantly with time since diagnosis) (F=14.3, p<0.001) No time effects found for anxiety (F=0.3, ns) nor depression (F=1.2, ns) No time effects found for DM-distress (F=3.0, ns), perceived seriousness (F=1.8, ns), self efficacy (F=0.2, ns), nor self management (F=0.0, ns) Some reported clinically relevant anxiety (HADS score ≥8; clinically definite scores ≥11) in group diagnosed < 1 y, but it seems to be effect of intensive treatment x time, because the intensive treatment group is significantly higher (mean scores, 6.8 vs 4.5, F=5.8, p<0.001). 2-3 y group mean scores = 5.0 vs 5.5, ns	Screen-detected persons generally do not experience difficulty with DM2 in the first 2-3y Early and intensive treatment can lead to relatively more anxiety and less self-efficacy in the first y after diagnosis, compared to less intensive treatment
ADDITION Study Eborall et al, 2007[190] *Fair*	Controlled clinical trial (embedded in the ADDITION RCT) 5,334	Population-based screening in the United Kingdom	15m	SSAI (anxiety) HADS (anxiety and depression) Lerman Cancer Worry Scale, adapted (DM-specific worry) Single item on general health	Comparison of screening attendees and control at the time of random BG (initial screen): NSD between groups in any outcome Comparison of patients invited for screening (attendees and non-attendees) and control: at 3-6m and 12-15m: NSD between groups in any outcome Immediate impact of initial positive screening test compared to negative screening test: poorer health; higher anxiety, depression, DM-specific worry (p all ≤ 0.05)	Screening has limited psychological impact on patients Being required to return for further tests after an initial positive random BG has small negative psychological impact of doubtful clinical significance

TABLE 8. STUDIES EXAMING THE ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design; N	Study population; Participant selection method	Follow-up	Measures used (operationalized outcomes)	Main results	Conclusions
ADDITION Study Eborall et al, 2007[189] *Not rated*	Cross-sectional, qualitative interviews 23	Sample of subjects scheduled for OGTT in the United Kingdom Unclear how sampled	0	Open-ended questions	Initial stages of screening processes: Most participants not very worried who tested positive on the first tests Prediagnostic test expectations: many accepted possibility of positive diagnosis Reactions after new diagnosis of DM2: tendency to downplay importance; all had plans to control the disease; most were grateful for screening program Diagnosed with IFG or IGT: many were confused by this diagnosis; most were unconcerned and unaware of this diagnosis as a risk factor for DM2 or CVD	Patients' perceptions changed at different stages of a stepwise screening program; patients adjust There is a tendency to downplay individual risk By the time of a positive diagnosis, most patients accepted the diagnosis and had plans to control their disease Persons with IGT/IFG were confused by this diagnosis and did not plan to change their lifestyle
Edelman et al, 2002[182] *Good*	Longitudinal cohort 1,253	All undiagnosed DM2 at baseline Population-based screening in the United States At screening, 56 DM2+ and 1177 nonDM2	1y	SF-36 MCS (health-related quality of life, mental component) SF-36 PCS (health-related quality of life, physical component)	NSD between DM and nonDM groups, nor between baseline and 1 y follow-up Baseline PCS: NonDM vs with newly-diagnosed DM (36.3 vs 35.6, p=0.67), ns Baseline MCS: NonDM vs with newly-diagnosed DM (49.6 vs 48.8, p=0.70), ns 1y follow-up PCS: NonDM vs with newly-diagnosed DM (35.2 vs 34.6, p=0.68), ns 1y follow-up MCS: NonDM vs with newly-diagnosed DM (48.2 vs 48.0, p=0.94), ns	HRQoL in persons with newly-diagnosed, screen-detected DM2 is similar to those who screen negative 1y after screening

TABLE 8. STUDIES EXAMING THE ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design; N	Study population; Participant selection method	Follow-up	Measures used (operationalized outcomes)	Main results	Conclusions
Farmer et al, 2003[183] *Good/fair*	Cohort 431	High risk of developing DM2 GP-identified siblings of DM2 family members in the United Kingdom	1y	SSAI-SF (anxiety) WBQ-12 (well-being) HAI (health anxiety)	Within group effect of time: Anxiety fell from 34.5 (95% CI 33.4-35.6) to 32.3 (31.2-33.4) at 1 y (p<0.0001) Well-being scores rose (improved) from 26.8 (26.0-27.4) to 27.4 (26.7-28.1, p=0.008) Anxiety (p=0.56) and well-being (p=0.79) over 1y did not differ between participants receiving a normal or an at-risk test result	Siblings of persons with DM2 have slightly elevated anxiety levels at the time of screening, but these levels decrease over 1y follow-up There were no differences in anxiety or well-being between subjects with a normal FPG and those with elevated glucose levels at 1y
Hoorn Study Adriaanse et al, 2004[178] *Fair*	Cohort 165	Newly diagnosed DM2 Screen-detected and GP-identified in Hoorn region of the Netherlands	2w 6m 1y	DSC-type 2 (perceived burden of DM) WBQ-12 (well-being) SF-36 (perceived health status)	DSC-type 2 scores (higher scores indicate more symptom distress): GPDM: 2w: 0.56; 6 m: 0.21; 1y: 0.26, p<0.001 SDM: 2w: 0.24; 6 m: 0.24; 1y: 0.29, p=0.093 SF-36 scores: Differences were statistically significant (worse) for GPDM group on SF-36 for Role Emotional (F=5.2, p=0.024), Mental Health (F=5.0, p=0.027), Vitality (F=3.9,p=0.049), compared with SDM GPDM General Health (F=3.7, p=0.028) and Vitality (F=4.5, p=0.012) scores improved significantly over time, compared with SDM Differences were statistically significant (worse) for GPDM group on WBQ-12 for General well-being, p=0.048, compared with SDM	The psychological impact of screening positive for DM2 is minimal and screening is generally not perceived as burdensome in this exploratory study
Hoorn Study Adriaanse et al, 2004[180] *Fair*	Cohort 259	Newly diagnosed DM2 vs high risk nonDM2 Population-based, targeted screening in Hoorn region of the Netherlands	2w 6m 1y	WBQ-12 (well-being) SF-36 (perceived health status)	2w after diagnosis: no significant mean differences between DM and nonDM on WBQ-12 nor SF-36 6m after diagnosis: statistically significant (worse) for DM for Role Physical (mean diff -8.2 [95% CI -16.2; -0.1], p=0.046) and Role Emotional (mean difference -7.9 [95% CI -15.3; -0.5], p=0.038), compared with nonDM 1y after diagnosis: no significant mean differences between DM and nonDM on WBQ-12 nor SF-36	Screening positive for DM2 does not have a substantial adverse psychological effect compared to nonDM subjects at up to 1y of follow-up

TABLE 8. STUDIES EXAMING THE ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design; N	Study population; Participant selection method	Follow-up	Measures used (operationalized outcomes)	Main results	Conclusions
Hoorn Study Adriaanse et al, 2005[179] *Fair*	Cohort 246	Newly-diagnosed DM2 vs high risk nonDM2 Population-based, targeted screening in Hoorn region of the Netherlands	2w 6m 1y	DSC-type 2 (DM related symptom distress) NWB Subscale of WBQ-12 (negative mood)	Total symptom distress (range 0-4) differences ns: DM (median scores at 2w, 6m, and 1y: 0.24, 0.24, 0.29) nonDM (0.15, 0.15, 0.18) No average difference nor change over time in negative well-being was found between DM and nonDM Negative well-being was significantly positively related with the total symptom distress score (regression coefficient beta = 2.86, 95% CI 2.15-3.58)	Persons with screen-detected, newly diagnosed DM2 have more hypoglycemic and fatigue symptoms than nonDM subjects at up to 1y follow-up
Nichols et al, 2004[185] P*oor (44% response rate)*	Cohort 273	Newly diagnosed DM2 vs undiagnosed DM2 Registry in the United States	1y	SF-12 MCS (health-related quality of life, mental component) SF-12 PCS (health-related quality of life, physical component)	Between groups at baseline: Mental health: 51.4 vs 51.9, p=0.406, ns 1y follow-up: No difference in change in health status (mental or physical health) in those who reported receiving a diagnosis (n=105) compared with those who did not (n=168). Adjusted for age difference between those receiving diagnosis (younger) and those not (67.0 vs 69.6, p=0.031). After adjustment, diagnosis was not associated with any difference in functional status, or with a change in physical (1.55 vs 0.05, p=0.233) or mental (-0.63 vs 0.01, p=0.598) health status	Receiving a diagnosis of DM2 after a change in diagnostic criteria does not adversely affect either mental or physical health status
Skinner et al, 2005[187] *Not rated*	Cross-sectional 1,339	High risk of developing DM2 GP, hospital, registry, and media identified in the United Kingdom	0	SSAI-SF (anxiety) Emotional Stability Scale of Big Five Inventory 44 (emotional stability) 3 scales from Diabetes Illness Representations Questionnaire - revised for study (DM related illness beliefs)	No effect of family history of DM, ethnic group, or recruitment methods on anxiety 45% of all participants reported "little to moderate" amounts of anxiety (mean 35.5, SD 11.6) Emotional stability was significantly (negatively) associated with anxiety, r=-0.45; n=930; p<0.001.	Screening for DM2 does not induce significant anxiety

Abbreviations: ADDITION Study, Anglo-Danish-Dutch Study of Intensive Treatment and Complication Prevention in Type 2 Diabetic Patients Identified by Screening in Primary Care; BG, blood glucose; CVD, cardiovascular disease; DM, diabetes; DM2, Type 2 diabetes; DSC-Type 2, Diabetes Symptom Checklist - Type 2 diabetes; FPG, fasting plasma glucose; GP, general practitioner; GPDM, General practitioner group with diabetes; HADS, Hospital Anxiety and Depression Scale; HAI, Health Anxiety Inventory; HRQoL, health-related quality of life; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; m, month; MCS, Mental Component Score; N, number of participants in study; nonDM, without diabetes; ns, not significant; NSD, no significant difference; NWB, Negative Well-Being subscale; OGTT, oral glucose tolerance test; PAID, Problem Areas in Diabetes scale; PCS, Physical Component Score; RCT, randomized controlled trial; SDM, Screened group with diabetes; SF-12, Medical Outcomes Study Short Form 12; SF-36, Medical Outcomes Study Short Form 36; SSAI-SF, Spielburger State-Trait Anxiety Inventory-Short Form; w, week; WBQ-12, Well-being Questionnaire-12; y, year.

Note: Selected studies omitted from this Summary Table; see Appendix Evidence Table B11 for full abstraction of all studies

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
α-glucosidase inhibitors				
Van de Laar et al, 2005[194] *Fair*	α-glucosidase inhibitors: acarbose (30 studies); miglitol (7 studies); voglibose (1 study) + 3 studies combined various DM2	NR	Acarbose: Any diabetes-related endpoint: RR 1.00 (0.81-1.23) vs placebo Microvascular disease: RR 0.91 (0.61-1.35) vs placebo Number of patients with side effects, odds ratio treated vs placebo; 3.37 (95% CI, 2.60 - 4.36)	NSD between acarbose and placebo with respect to morbidity and mortality
Van de Laar et al, 2007[193] *Good*	α-glucosidase inhibitors: acarbose (5 studies) IGT and IFG	NR	Gastrointestinal (flatulence, diarrhea): OR 3.5 (2.7-4.4) vs placebo	Acarbose causes significant gastrointestinal side effects compared to placebo
ACE inhibitors and ARBs				
McDonald et al, 2005[197] *Good*	ARBs At risk for CV events	NR	MI pooled effect: OR=0.94 (0.75 - 1.16)	ARBs are not associated with an increased risk of MI when compared with placebo.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Strippoli et al, 2006,[195] 2004[196] *Fair*	ACE inhibitor ARBs placebo DM1: 20 studies DM2: 23 studies Mixed DM population: 6 studies	Total withdrawals: 0.2 to 1.0% Withdrawal due to AEs: NR	ACE inhibitors, I vs C: All-cause mortality (any dose) 12.3%; 12.7% (p>0.05) CV mortality 5.8%; 5.9%(p=0.6) Doubling of serum creatinine 3.0%; 4.3% (p=0.05) End-stage kidney disease 0.85%; 1.5% (p=0.02) Cough (vs placebo): 3.17 (2.29, 4.38) Hyperkalemia: NSD vs placebo ARBs: All-cause mortality 13.7%; 15.6% (p=0.9) Doubling of serum creatinine 15.1%; 21.5% (p=0.004) End stage kidney disease 13.3%; 19.3% (p=0.001) Cough (vs placebo): 4.93 (1.00, 24.35)	ACE inhibitors vs ARBs: Based on indirect analysis no significant differences for any outcome, including: all-cause mortality, end-stage renal disease, doubling of serum creatinine concentration, progression from microalbuminuria to macroalbuminuria or regression from microalbuminuria to normoalbuminuria. ACE inhibitors or ARBs vs placebo: All-cause mortality: ACE inhibitors, but not ARBs, were associated with a significant reduction in all-cause mortality; end-stage renal disease and doubling of serum creatinine concentration: weak evidence of reduced risk with ACE inhibitor use with no significant difference in risk for ARBs; both ACE inhibitors and ARBs associated with significantly reduced risk of progression from microalbuminuria to macroalbuminuria and increased rate of regression from microalbumunuria to normoalbuminuria.
Velazquez-Armenta et al, 2007[198] *Fair*	ARBs Pregnancy	NR (case series)	Favorable pregnancy outcomes: 57.8% (37 cases) Unfavorable pregnancy outcomes (eg: abnormalities including limb and face deformations, enlarged kidneys, anuria, severe hypotension, etc): 42.2% (27 cases) ARBs in this group included valsartan, losartan, candesartan, and irbesartan Duration of treatment during pregnancy among women who had adverse fetal outcomes was 26.3±10.5 weeks vs 17.3±11.6 weeks for those who had favorable outcomes (p=0.04)	Exposure to ARBs for a period longer than the first trimester of pregnancy appears to be associated with an increased risk of adverse fetal outcomes (p=0.04)
Verdecchia et al, 2005[199] *Fair*	ARBs At risk for CV events	NR	MI: OR 0.96 (95% CI, 0.84 - 1.10), p=0.57 CVD mortality: OR 0.91 (95% CI, 0.83 - 0.99), p=0.042	ARBs are not associated with an increased risk of MI when compared with placebo.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Aspirin				
Berger et al, 2006[201] *Good*	Aspirin Primary prevention of cardiovascular events	NR	Bleeding in men: OR 1.72 (1.35 - 2.20; p<0.001) Bleeding in women: OR 1.68 (1.13 - 2.52; p=0.01) Stroke in men: OR 1.13 (0.96 - 1.33) Stroke in women: OR 0.83 (0.70 - 0.97) Ischemic stroke in men: OR 1.00 (0.72 - 1.41) Ischemic stroke in women: OR 0.76 (0.63 - 0.93) Hemorrhagic stroke in men: OR 1.69 (1.04 - 2.73) Hemorrhagic stroke in women: OR 1.07 (0.42 - 2.69)	Reduced risk of CV events for men and women with aspirin use; significant increase in bleeding risk for both groups; NSD in CV or all-cause mortality
McQuaid et al, 2006[200] *Good*	Aspirin or Clopidogrel For cardiovascular prophylaxis	Aspirin: All events: RR=1.16 (05% CI, 0.94 - 1.44) GI events: RR=1.26 (0.94 - 1.70) non-GI events: RR=0.84 (0.55 - 1.28)	Aspirin : Major bleeding: RR=1.71 (95% CI, 1.41 - 2.08) Major GI bleeding: RR=2.07 (1.61 - 2.66) Intracranial bleeding: RR=1.65 (1.06 - 5.99) Dyspepsia: RR=1.09 (0.97 - 1.22) Diarrhea: RR=3.30 (1.42 - 7.66) Constipation: RR=1.98 (1.14 - 3.44) Rash: RR=0.77 (0.38 - 1.58) 769 patients need to be treated with aspirin to cause 1 additional major bleeding episode annually No study compared clopidogrel with placebo	Low-dose aspirin associated with an increase in risk of major bleeding (~70%; NNT: 796) relative to placebo/no use Compared to clopidogrel, aspirin associated with higher risk of GI bleeding (NNT 883 to prevent one major GI bleeding episode)
Beta-blockers				
Wiysonge et al, 2007[202] *Good*	Beta-blocker (not stratified; including atenolol, propranolol, oxeprenolol, metoprolol) Placebo Hypertension, >18 years	Total withdrawals NR Withdrawals due to AEs I vs C 18.2% vs 8.6%; p=0.1 RR 2.34 (0.84-6.62)	I vs C: Total mortality 5.0%; 5.2% (p=0.8) CHD 3.5%; 3.7% (p=0.3) Stroke 1.8%; 2.3% (p=0.02) CV mortality 2.6%; 2.9% (p=0.4) CV disease 5.7%; 6.4% (p=0.01)	No significant difference between beta-blockers and placebo in total mortality or CHD. Use of beta-blockers was associated with a significantly lower risk of stroke and CV events, relative to placebo.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Hypoglycemic agents				
Bolen et al 2007[203] *Good*	Various oral hypoglycemic agents: pioglitazone rosiglitazone metformin sulfonylureas repaglinide nateglinide acarbose placebo DM2	Total withdrawals: I vs C Pioglitazone: NR Rosiglitazone 3.8-6.3% vs 2.7-12.0% Metformin NR Sulfonylurea 2.4% vs 7.9% (1 study) Meglitinide (repaglinide or nateglinide) NR Acarbose NR Withdrawals due to AEs: I vs C Pioglitazone 1.1-3.0% vs 2.4-4.8% Rosiglitazone 0.9%-7.4% vs 1.2-10.3% Metformin 3.0-15.4% vs 0-17.2% Sulfonylurea 0-14.3% vs 1.9-30.4% Meglitinide (repaglinide or nateglinide) 1.5-7.6% vs 3.0-4.3% Acarbose 2.5% vs 5.3% and 58.1% vs 44.8% (2 studies; rate varied widely)	I; C Pioglitazone: Hypoglycemia 0.6-11.0%; 0-11% Edema 3.0-13.6%; 0-7.5% CHF 3.6-14.0%; 0.6-16.0% ALT elevations 0-6%; 0-6.0% AST elevations 0-1%; 1% Rosiglitazone: Hypoglycemia 3.4-12%; 2.0-6.0% Edema 6.0-18.0%; 3% CHF 4.1-13.6%; 0-2.5% ALT elevations 0-1.2%; 0-1.1% Metformin: Mortality (1 study) 0.3%; 0% Hypoglycemia 1.3-13.4%; 0-10.3% Sulfonylurea: Hypoglycemia 0-17.7%; 0-1.2% CHF 4.2%; 3.5% (1 study each) Meglitinide (repaglinide or nateglinide): Hypoglycemia 0-12.8%; 0-11.0% Acarbose: Hypoglycemia 9.7%; 10.3% (1 study each)	No clear conclusions regarding all-cause mortality associated with metformin + second generation sulfonylurea vs metformin and/or a second generation sulfonylurea could be drawn due to conflicting results and/or lack of evidence. The effect of metformin + second generation sulfonylurea vs metformin or a second generation sulfonylurea on CV mortality was unclear; other oral diabetes medications lack adequate evidence to draw conclusions No conclusions can be made regarding CV morbidity due to limited number of studies; pioglitazone+metformin associated with improved CV morbidity relative to placebo/diet
Gangji et al, 2007[204] *Good*	Glyburide, other secretagogues, insulin DM2	NR; loss to follow-up ranged from 0 to 37%	Glyburide compared to other secretagogues Hypoglycemia: RR 1.52 (1.21-1.92); compared to other sulfonylureas, RR 1.83 (1.35-2.49)) Cardiovascular risk: RR 0.84 (0.56-1.26) Death: RR 0.87 (0.70-1.07)	Glyburide caused more hypoglycemia than other secretagogues and other sulfonylureas, but was not associated with increased risk of cardiovascular events or death.
Saenz et al, 2005[205] *Good*	Metformin DM2	NR	Metformin; comparator All-cause mortality: 0.51%; 0.0% (p=0.3) Hypoglycemia: 2.7%; 0.5% (p=0.2) No cases of lactic acidosis	Pooled data from trials of various active interventions, placebo and/or diet changes found no difference in rates of all-cause mortality or ischemic heart disease.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Salpeter et al 2003[207], 2006[206] *Good*	Metformin DM2	NR	Fatal or non-fatal lactic acidosis: 0% Estimated upper limit 95% confidence interval for incidence of lactic acidosis metformin vs non-metformin (cases/100,000 patient-years): 6.3 vs 7.8 No other AEs reported Control group: 0% with various hypoglycemic agents as comparators	No evidence of an association between metformin use and lactic acidosis relative to other anti-hyperglycemic agents
Setter et al, 2003[208] *Poor*	Metformin DM2	Unable to tolerate as a result of prolonged adverse effects: <5%	Episodes of severe hypoglycemia: 'negligible' (no other data) Lactic acidosis: rate 8 cases/100,000 person-years (1 study)	Very limited data found that potentially fatal lactic acidosis can be associated with metformin use, although absolute risk is low.
Statins				
Bonovas et al, 2007[209] *Fair*	Pravastatin Cardiovascular therapy for different ages	NR	Cancer risk: random-effects model (RR 1.06 (95% CI, 0.97 - 1.14)) Cancer risk as age increases: meta-regression, p=0.006	Possible association between pravastatin use and increased cancer risk in the elderly. Findings need to be replicated.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Law et al, 2006[211] *Fair-Poor*	Various statins Those prescribed statin treatment (details NR)	NR	Peripheral neuropathy (OR from 4 cohort studies): 1.8 (1.1 - 3.4) Rhabdomyolysis: Incidence per 100,000 person years Cohort studies: Cervistatin: 46 (13 - 120) Statins (without cervistatin): 1.6 and 6.5 (2 studies) Gemfibrozil: 28 (6-81) FDA Reporting System: Cervistatin: 21 (19 - 25) Statins (without cervistatin): 0.70 (0.62 - 0.79) Mortality estimated at 10% of incidence Treated minus placebo, Per 100,000 person years Rhabdomyolysis: 1.6 (-2.4 - 5.5) Myopathy: 5 (-17 - 27) Minor muscle pain: 190 (-38 - 410) Elevated Creatine kinase: 23 (-4 - 50) Elevated ALT (single measure): 100 (64 - 140) Elevated ALT (2 consecutive measures): 70 (50 - 90)	Despite high risk with cervistatin, incidence of rhabdomyolysis is low in patients taking simvastatin, lovastatin, atorvastatin, provastatin, or fluvastatin - estimated as 3 per 100,000 person-years. Myopathy attributable to these statins is also rare (11 per 100,000 person years). Most muscle symptoms in patients taking statins are not attributable to the statins.
McClure et al, 2007[210] *Good*	Statins Those prescribed statin treatment (details NR)	Discontinuation due to AEs: OR (95% CI) Overall (w/o cervastatin) : OR 0.88 (0.84 - 0.93) Lovastatin: 1.10 (0.98 - 1.24) Pravastatin: 0.79 (0.74 - 0.84) Simvastatin: 1.00 (0.89 - 1.11) Fluvastatin: 0.93 (0.75 - 1.16) Atorvastatin: 0.93 (0.75 - 1.14) Rosuvastatin: 0.68 (0.26 - 1.77) Cervastatin: 1.45 (0.98 - 2.16)	OR (95% CI) Rhabdomyolysis (w/o cervistatin): 1.59 (0.54 - 4.70) Myositis (w/o cervistatin): 2.56 (1.12 - 5.85) Myositis (cervistatin): 3.36 (0.59 - 19.3) Creatine kinase (w/o cervistatin): 1.11 (0.78 - 1.59) Creatine kinase (cervistatin): 2.93 (1.08 - 7.92) Myalgia (w/o cervistatin): 1.09 (0.97 - 1.23) Myalgia (cervistatin): 1.74 (0.51 - 5.91)	Overall, discontinuation of statin therapy was no worse than placebo. Risks of muscle related AEs in agreement with known risks of statins; rates are much higher with ceruvistatin than other statins.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Silva et al, 2006[212] *Fair*	Statins Those prescribed statin treatment or placebo	NR	Risk of any AE: OR 1.4 (1.09 - 1.80), p=0.008 vs placebo, NNH 197 Risk of clinical CV event: OR 0.74 (0.69 - 0.80), p<0.001, NNT = 27 Treating 1000 pts with statin would prevent 37 CV events, and 5 AEs would be observed. Serious events (creatine kinase > 10x upper limit of rhabdomyolysis) are infrequent, NNH = 7428 Nonurgent AEs (myalgia and liver function tests) responsible for 2/3 of AEs reported in trials: 0.48 (0.25 - 0.7), NNH = 209 Rate of liver failure: 1 per 100,000 person years of statin use. Person years for any event/serious event: Placebo: 181/48	Statin therapy in associated with greater odds of AEs compared with placebo, but with there is also substantial clinical benefit. Similar rates of serious AEs was observed between statins and placebo.
Thiazolidinediones				
Norris et al, 2006[213] *Good*	Pioglitazone (pio) 7.5-45 mg qd Rosiglitazone (rosi) 4-12 mg qd DM2, pre-DM, the metabolic syndrome	Total withdrawals, I v C (placebo): pio: 7.0-33.0% v 2.4-20.0%; pooled RD v placebo -1.0% (-3.0 - 1.0%) rosi: 0-27.0% v 0-38.4%; pooled RD v placebo -3.0% (-9.0 - 2.0%) Withdrawals due to AEs, I v C (placebo): pio: 4.8% v 4.5%; pooled RD 0% (-2.0 - 2.0%) rosi: 4.9% v 7.2%; pooled RD v placebo -2% (-4% - -1%)	Thiazolidinedione; placebo Pioglitazone: Cardiac-related events: 3.6%; 6.3% CHF: 11.0%; 8.0% (p<0.05) Peripheral edema: 0-22.0%; 0-16.0% Abnormal LFT: 0.77%-2.4%; 1.3% Hypoglycemia: 0-28.0%; 0-20.0% Rosiglitazone Peripheral edema: 4.1-6.6%; 1.6% (p<0.05 (4mg bid dose only, rosiglitazone rate 6.6%) Abnormal LFT: 0-0.6%; 0.0%	Total withdrawals and withdrawals due to AEs were similar in each of the rosi, pio, and placebo groups. The incidence of edema was significantly greater in both rosi and pio, than placebo. The risk difference for hypoglycemic events between placebo and each of rosi and pio was not significant. Weight gain was greater with both rosi and pio compared to placebo.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Richter et al, 2007[215] *Fair*	Pioglitazone RCTs in adults with DM2 and trial duration ≥ 24w	Total withdrawals: NR % drop-outs due to AEs; similar between pio and comparators	Decrease in A1c: consistent in 6 studies which examined this outcome compared to : range 0.5 to 0.75 g/dl Body weight: increased in 15 studies compared to various comparators: up to 3.9 kg Hypoglycemic episodes (%): somewhat lower rates with pio than various active controls Edema: relative risk pio vs various other comparators: 2.86 (95% CI, 2.14 - 2.52)	Pioglitaone appears to decrease A1c, increase body weight, and increase edema compared to various other active therapies or placebo.
Richter et al, 2007[214] *Fair*	Rosiglitazone RCTs in adults with DM2 and trial duration ≥ 24 weeks	Total withdrawals: NR Withdrawals due to AEs: I 2.7 to 11.6%, C: 2.0 to 14.9% (no pooled estimates available; no between-group-values available)	Edema: OR 2.27 (95% CI, 1.83 - 2.81) Fractures, CVD events, CHF, PVD, mortality: data reported from the ADOPT trial only Severe hypoglycemic episodes: I 0-5.4%, C 0-2.9%; no pooled data and no statistics	Rates of edema are increased with rosiglitazone compared with various other drugs or placebo. The ADOPT trial suggests that fractures rates in women may be increased.
Singh et al, 2007[216] *Fair*	Rosiglitazone RCTs in DM2 or IGT and trial duration ≥ 12 months	NR	Relative risk 95% CI) rosiglitazone vs comparator: MI: 1.42 (1.06 - 1.91) Heart failure: 2.09 (1.52 - 2.88) CV mortality: 0.90 (0.63 - 1.26)	Rosiglitazone use for 12 or more months increases the risk of MI and heart failure, without significantly increasing the risk of CV mortality.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Weight loss drugs				
Li et al, 2005[218] *Good*	Sibutramine, phentermine, diethylpropion, orlistat, fluoxetine, bupropion, topiramate, sertraline, zonisamide Those prescribed obesity management treatment	NR	Pooled OR (95% CI): <u>Orlistat</u>: Diarrhea 54.85 (44.88 - 67.48) Flatulence 3.72 (3.16 - 4.39) Bloating, abdominal pain, dyspepsia 1.55 (1.18 - 2.06) Headache 1.18 (0.68 - 2.05) <u>Fluoxetine</u>: Nervousness, sweating tremors 7.85 (3.87 - 17.63) Nausea, vomiting 3.27 (1.94 - 5.67) Fatigue, asthenia, hypersomnia, somnolence 2.83 (1.82 - 4.45) Insomnia 2.19 (1.10 - 4.58) Diarrhea 1.86 (1.10 - 3.23) Urticaria, pruritus, rash 1.67 (0.53 - 5.65) Headache 1.35 (0.91 - 2.03) <u>Bupropion</u>: Dry mouth 3.26 (1.71 - 6.64) Diarrhea 1.37 (0.52 - 4.01) Constipation 1.31 (0.72 - 2.44) Upper respiratory problems 1.22 (0.88 - 1.69) <u>Topriamate</u>: Paresthesia 20.18 (13.99 - 29.67) Taste perversion 11.14 (2.80 - 23.57) Central nervous system effects 3.97 (2.90 - 5.49) Constipation 3.96 (1.77 - 9.77) Dry mouth 3.13 (1.59 - 6.55) Upper abdominal symptoms 1.76 (1.27 - 2.47) Fatigue 1.36 (1.03 - 1.80) Upper respiratory problems 1.32 (0.87 - 1.99)	Sibutramine: Effects on BP varied; A1c and fasting blood glucose decreased; heart rate was consistently elevated by 4 beats per minute. Orlistate was associated with diarrhea, abdominal pain, and dyspepsia; it was unclear if these improved over time. Fluoxitine: nervousness, sweating, tremors, nausea and vomiting, and insomnia increased significantly compared with placebo. There were few studies with long-term adverse effects data.

TABLE 9. SYSTEMATIC REVIEWS EXAMINING THE ADVERSE EFFECTS OF TREATMENT (KQ5)

Drugs Study, Year, *Quality*	Intervention; Population	Total withdrawals; Withdrawals due to adverse events	Adverse events: Intervention group	Conclusions
Norris et al, 2005[217] *Good*	Fluoxetine, orlistat, sibutramine Placebo DM2	Total withdrawals NR Withdrawals due to AEs fluoxetine v control: 1-9% v 0-2% orlistat v control: 0.3-22% v 0.5-28% sibutramine: 3-7% v 0%(1 study)	Data based on 1 study (no pooled data available) Orlistat; placebo Hypoglycemia: 7-17%; 3-10.0% GI events: 65-80%; 27-62% Fluoxitine; placebo Tremor: 5-15%; 0-3% Somnolence: 11-22%; 4-7% Sweating: 28%; 11% Sibutramine; placebo Palpitations 41%; 29% Dry mouth: 38%; 223%	Gastrointestinal adverse effects were common with orlistate; tremor, somnolence, and sweating with fluoxetine; and palpitations with sibutramine.

Abbreviations: ACE, Angiotensin-converting enzyme; ADOPT, A Diabetes Outcomes Progression Trial; AE, adverse event; ALT, Alanine aminotransferase; ARBs, Angiotensin II Receptor Blockers; AST, Aspartate aminotransferase; bid, twice daily; C, control group; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes; DM1, type 1 diabetes; DM2, type 2 diabetes; FDA, Food and Drug Administration; GI, gastrointestional; I, intervention group; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LFT, liver function tests; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; NSD, no significant difference; OR, odds ratio; pio, pioglitazone; PVD, peripheral vascular disease; qd, daily; RCT, randomized controlled trial; RD, risk difference; rosi, rosiglitazone; RR, relative risk; y, years.

TABLE 10. OUTCOMES TABLE

Number needed to screen for type 2 diabetes to prevent one adverse event

		Tight glycemic control to prevent one case of blindness in one eye (screening 1000 people with given prevalence)			Tight blood pressure control to prevent one CVD event (screening 1000 hypertensive people with given prevalence)		
Prevalence of undiagnosed disease (%)	Population	Increase in persons with tight glycemic control due to screening (%)	Cases of blindness averted*	NNS	Increase in persons with tight blood pressure control due to screening (%)	CVD events averted†	NNS
5.0 years of additional treatment							
2.8	Standardized prevalence in US‡	25	0.03	32,841	25	0.26	3,810
		50	0.06	16,420	50	0.53	1,905
		90	0.11	9,122	90	0.95	1,058
3.6	Standardized prevalence, US non-Hispanic blacks‡	25	0.04	25,543	25	0.34	2,963
		50	0.08	12,771	50	0.68	1,481
		90	0.14	7,095	90	1.22	823
5.8	Crude prevalence, US, ≥ 65y‡	25	0.06	15,854	25	0.54	1,839
		50	0.13	7,927	50	1.09	920
		90	0.23	4,404	90	1.96	511
6.0	Prevalence estimated for prior review	25	0.07	15,326	25	0.56	1,778
		50	0.13	7,663	50	1.13	889
		90	0.23	4,257	90	2.03	494
2.5 years of additional treatment							
2.8	Standardized prevalence in US‡	25	0.02	65,681	25	0.13	7,619
		50	0.03	32,841	50	0.26	3,810
		90	0.05	18,245	90	0.47	2,116
3.6	Standardized prevalence, US non-Hispanic blacks‡	25	0.02	51,086	25	0.17	5,926
		50	0.04	25,543	50	0.34	2,963
		90	0.07	14,190	90	0.61	1,646
5.8	Crude prevalence, US, ≥ 65 years‡	25	0.03	31,708	25	0.27	3,678
		50	0.06	15,854	50	0.54	1,839
		90	0.11	8,808	90	0.98	1,022
6.0	Prevalence estimated for prior review	25	0.03	30,651	25	0.28	3,556
		50	0.07	15,326	50	0.56	1,778
		90	0.12	8,514	90	1.01	988

TABLE 10. OUTCOMES TABLE

Number needed to screen for prediabetes to prevent 1 case of diabetes after 3 years

Prevalence of IGT or IFG (%)	Population	Lifestyle intervention to prevent one case of diabetes (screening 1000 people with given prevalence)§			Metformin to prevent one case of diabetes (screening 1000 people with given prevalence)‖		
		Increase in persons adhering to intervention (%)	Cases of diabetes delayed	NNS	Increase in persons adhering to intervention (%)	Cases of diabetes delayed	NNS
15.0	IGT only, total US population¶	25	2.39	418	25	1.28	782
		50	4.79	209	50	2.56	391
		90	8.61	116	90	4.60	217
26.0	IFG only, total US population‡	25	4.15	241	25	2.22	451
		50	8.29	121	50	4.43	226
		90	14.93	67	90	7.98	125
40.0	Estimate IFG and/or IGT#	25	6.38	157	25	3.41	293
		50	12.76	78	50	6.82	147
		90	22.97	44	90	12.28	81

* Relative risk reduction 0.29 over 5 years, based on incidence of retinal photocoagulation in one eye, from United Kingdom Prospective Diabetes Study; rate of blindness in no-treatment group 1.5% over five years[223]

† Relative risk reduction 0.50 over 5 years, based on the Hypertension Optimal Treatment trial; usual treatment 5-year incidence 7.5%[94]

‡ Prevalence data from National Health and Nutrition Examination Survey, 2002 data, IFG 100-126 mg/dl [2]

§ Relative risk reduction based on the Diabetes Prevention Program: 58%; 38% achieved weight loss goal of 7% at end of 3-year follow-up (intention-to-treat analysis); control rate 11%[79]

‖ Relative risk reduction based on Diabetes Prevention Program: 31%, with compliance rates (80+% of medications taken) 77% in control, 72% in intervention group[79]

¶ Based on National Health and Nutrition Examination Survey, 1994 data[242]

From National Institute of Diabetes and Digestive and Kidney Fact Sheet, 1994 data[241]

Abbreviations: CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NNS, number needed to screen.

TABLE 11. SUMMARY OF EVIDENCE

Number of Studies: *Overall Quality Rating*	Design; References	Limitation	Consistency	Primary Care Applicability	Summary of Findings
Key Question 1: Overall effect of screening on final outcomes					
3 studies *Poor*	Case–control and cross-sectional studies[84-86]	Data were limited; studies considered microvascular complications only.	Studies were consistent.	Case–control study was representative of a primary care population, but results did not represent population-level results from a screening program. Fair-quality cross-sectional study was a non–US population in an area of high screening rates and national registries; however, an unknown percentage was clinically detected.	Both fair-quality studies demonstrated no benefit for screening: Case–control study: Patients with 1 or more glucose screening event in 10 years had a 13% reduction in risk of severe microvascular T2DM complications. Cross-sectional study: No significant differences between T2DM population and general Swedish population (where there is a high level of screening for T2DM) in most measures of visual acuity. One poor-quality study showed NSD.
Key Question 2: Diabetes treatment					
8 studies *Fair*	RCTs with diabetes vs. nondiabetes (subgroup analyses); RCTs with duration of T2DM ≤1 y[95-98, 103, 104, 115-117]	Several studies were probably underpowered for the diabetes subgroup. Because diabetes as a cardiovascular risk factor was itself an entry criterion for some studies, baseline characteristics differed between the diabetes and nondiabetes subgroups.	Studies generally showed no evidence of significant differential effect between diabetes and nondiabetes subgroups.	Studies were representative of a primary care population, but results did not represent population-level results from a screening program.	Persons with T2DM without known CVD seem to benefit from aggressive lipid-lowering treatment as much as persons without T2DM with known CVD. There is little strong evidence that specific antihypertensive drugs benefit persons with T2DM more than those without. Persons with T2DM seem to benefit from a lower BP target than persons without. Fair evidence suggests a marginal benefit of aspirin for primary prevention of CVD, although no clear evidence suggests that those with diabetes benefit more than other subgroups at high-risk for CVD.
Key Question 3: Prediabetes treatment					
11 studies *Fair*	RCTs[79-81, 136, 138, 148, 154-157, 161]	Mean follow-up, approximately 3 years; longest follow-up, 7 years; only 3 studies examined long-term health outcomes.	Lifestyle and drug interventions consistently produced a decrease in incidence of T2DM	Trials consisted of highly selected participants.	Intensive lifestyle and pharmacotherapeutic interventions reduce the progression of prediabetes to T2DM at follow-up up to 7 years. Few data exist on the effect of these interventions on cardiovascular events, death, or other long-term health outcomes.

TABLE 11. SUMMARY OF EVIDENCE

Number of Studies: *Overall Quality Rating*	Design; References	Limitation	Consistency	Primary Care Applicability	Summary of Findings
Key Question 4: Adverse effects of screening					
8 studies *Fair-poor*	Cohort and cross-sectional studies[178-180, 182, 183, 185, 187, 190]	All observational studies; predominantly white study samples were composed of volunteers; short follow-up.	It is difficult to compare results across studies because of heterogeneous outcome measures and control groups; however, no serious adverse effects were noted.	Studies included persons at high risk for T2DM, so results may not be applicable to primary care populations.	Data were sparse on the psychological effects of screening for T2DM and no available data suggested significant adverse effects at up to 1-year follow-up. No study reported serious, long-term, adverse effects of a new diagnosis of T2DM.
Key Question 5: Adverse effects of treatment					
24 studies *Fair*	Systematic reviews[193-195, 197-206, 208-218]	Reviews were almost entirely based on trials of short to moderate duration; long-term data were lacking.	Not applicable; different drugs were examined in each review.	Included studies were largely trials of selected populations with limited applicability to real-world, primary care populations.	Acarbose: NSD in death from placebo; gastrointestinal side effects common Metformin: NSD in death, hypoglycemia, lactic acidosis vs. placebo or diet ACE-I: significant increase in cough vs. placebo β-Blockers: increase in withdrawals secondary to adverse events vs. placebo; NSD in total deaths Rosiglitazone: new data on potential for increased risk for cardiac events and heart failure

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; BP, blood pressure; CVD, cardiovascular disease; NSD, no significant difference; OR, odds ratio; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

Appendices

Appendix A

Definitions and Abbreviations

APPENDIX A1. DIABETES DEFINITIONS

Asymptomatic type 2 diabetes mellitus:

Persons without:

- Symptoms directly related to hyperglycemia such as polyuria or polydipsia
- Symptoms related to conditions known to be associated with diabetes such as foot ulcers, ischemic heart disease, or infections

Pre-diabetes:*

- Impaired fasting glucose (IFG): An intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having fasting plasma glucose levels ≥ 100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l).
- Impaired glucose tolerance (IGT): An intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having 2-h values of the 75-gram oral glucose tolerance test (OGTT) of ≥ 140 mg/dl (7.8 mmol/l) but < 200 mg/dl (11.1 mmol/l).

Type 2 diabetes mellitus (previously referred to as non-insulin dependent diabetes or adult-onset diabetes):*

A metabolic disease characterized by hyperglycemia resulting from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. Criteria for diagnosis are any of the following:

- Symptoms of diabetes plus causal plasma glucose ≥ 200 mg/dl
- Fasting plasma glucose ≥ 126 mg/dl
- 2-hour post 75-gram oral glucose tolerance test plasma glucose ≥ 200 mg/dl

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

*__Reference:__ American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus – Position Statement. *Diabetes Care*. 2007;30(Suppl 1):S42-S47.

APPENDIX A2. ABBREVIATIONS AND ACRONYMS

Abbreviation	Terminology
AA	African-American
AASK	AASK, African-American Study of Kidney Disease and Hypertension Trial
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitors
ADA	American Diabetes Association
AEs	Adverse events/effects
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AGI	Alpha-glucosidase inhibitor
AIIRA	Angiotensin II receptor antagonists
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALLHAT-LLA	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Arm
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ARBs	Angiotensin II receptor blocker
ARR	Absolute risk reduction
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
-LLA	- Lipid Lowering Arm
AST	Aspartate aminotransferase
AUC	Area under the curve
BG	Blood glucose
bid	Two times daily
BIP	Bezafibrate Infarction Prevention Trial
BMI	Body mass index
BP	Blood pressure
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
C	Control group
CABG	Coronary artery bypass graft
CARDS	Collaborative AtoRvastatin Diabetes Study
CD	Controlled diet
CDC	Center for Disease Control and Prevention
CDE	Conventional dietary education
CE	Cost effectiveness
CHD	Coronary heart disease
CHF	Congestive heart failure
COER	Controlled-onset extended-release
CONVINCE	Controlled ONset Verapamil Investigation of Cardiovascular Endpoints Trial
CORE	Center for Outcomes REsearch
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DBT	Target blood pressure
DCCT	Diabetes Control and Complications Trial
DM	Diabetes
DM1	Type 1 diabetes mellitus
DM2	Type 2 diabetes mellitus
DPP	Diabetes Prevention Program
DPS	Finnish Diabetes Prevention Study
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
DSC-Type 2	Diabetes Symptom Checklist - Type 2
EF	Ejection fraction
EKG (or ECG)	Electrocardiogram
ESRD	End-stage renal disease
FBG	Fasting blood glucose
Fin-D2D	National Type 2 Diabetes Prevention Program in Finland
FPG	Fasting plasma glucose
GI	Glucose intolerance
GPDM	General practitioner group with diabetes

APPENDIX A2. ABBREVIATIONS AND ACRONYMS

Abbreviation	Terminology
HADS	Hospital Anxiety and Depression Scale
HAI	Health Anxiety Inventory
HCTZ	Hydrochlorothiazide;
HDL	High density lipoprotein
HMO	Health maintenance organization
HOPE	Heart Outcomes Prevention Evaluation study
HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
HR	Hazard ratio
HRQoL	Health Related Quality of Life questionnaire
HT	Hypertension
Hx	History
I	Intervention group
IDNT	Irbesartan Diabetic Nephropathy Trial
IGT	Impaired glucose tolerance
IFG	Impaired fasting glucose
ITT	Intention to treat analysis
JMIC-B	Japan Multi-center Investigation for Cardiovascular Diseases-B
LDL	Low density lipoprotein
LE	Life expectancy
LEA	Lower extremity amputation
LFT	Liver function test
LIFE	Losartan Intervention for Endpoint Reduction Trial
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
LSM	Lifestyle Modification
LTPA	Leisure time physical activity
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LY	Life year
m	Months
MCS	Mental Component Score
MI	Myocardial infarction
NA	Not applicable
NCEP	National Cholesterol Education Project
NDE	New dietary education
NFG	Normal fasting glucose
NG	Normoglycemic
NGT	Nondiabetic or normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
NICOLE	Nisoldipine In Coronary Artery Disease in Leuven
nonDM	Without diabetes
NNT	Number needed to treat
NR	Not reported
NSD	Not significant
NSD	No significant difference
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
OP	Outpatient
OR	Odds ratio
PA	Physical activity
PAID	Problem Areas in Diabetes scale
PART2	Prevention of Atherosclerosis with Ramipril Therapy
PCS	Physical Component Score
preDM	Prediabetes
PPG	Postprandial plasma glucose
PPP	Primary Prevention Project trial
PREVENT	Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial

APPENDIX A2. ABBREVIATIONS AND ACRONYMS

Abbreviation	Terminology
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk trial
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
q	Every
qd	Daily
QOL	Quality of life
RCT	Randomized controlled trial
RD	Risk difference
RENAAL	Randomized Evaluation of Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan
RF	Reduced fat
RR	Relative risk
RRR	Relative risk reduction
RTI	Research Triangle International
SBP	Systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SD	Standard deviation
SDM	Screened group with diabetes
SF-12	Medical Outcomes Study Short Form 12
SF-36	Medical Outcomes Study Short Form 36
SRQ	Symptom Risk Questionnaire
SSAI-SF	Spielburger State-Trait Anxiety Scale-Short Form
STOP-NIDDM	Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus
SYST-EUR	Systolic Hypertension-Europe trial
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
tid	Three times daily
TZDs	Thiazolidinediones
UAP	Unstable angina pectoris
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
W	White
WBQ-12	Well-being Questionnaire 12
WHI	Women's Health Initiative
WHO	World Health Organization
wks	Weeks
WOSCOS	West of Scotland Coronary Prevention Study
XENDOS	Xenical in the Prevention of Diabetes in Obese Subjects
y	Year

Appendix B

Evidence Tables

APPENDIX B1. EVIDENCE TABLE ON RE-SCREENING INTERVALS (SQ1)

Author, Year Quality assessment	Study objective	Country/ Setting	Study design	N	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection	Population	Intervention
Lindeman, 2003[42] *Fair*	To determine frequency necessary for screening healthy elderly persons (>65 y) using FSG	New Mexico, US	Longitudinal, prospective cohort	299	12.4 y (mean)	New Mexico Aging Process Study (NMAPS) participants > age 65 y at study entry Healthy (defined as not meeting exclusion criteria)	Overt clinical conditions, (eg, coronary heart disease, diabetes mellitus, significant peripheral vascular disease, hepatic disease) History of internal cancer in last 10 y Hepatitis On prescription medication, except for thyroid replacement therapy and antihypertensive medications to control systolic blood pressure initially < 180 mm Hg or diastolic pressure < 100 mm Hg	Community-based volunteers	Upper, middle class 97% Caucasian; 3% Hispanic 117 Men; 182 Women Mean age 71.6 (4.8 SD)	NMAPS participants followed with annual FSG concentrations and BMI Started in 1980, some followed up to 18 y (mean 12.4 y)

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; DM2, type 2 diabetes; FSG, fasting serum glucose; N, number of study participants; NMAPS, New Mexico Aging Proceess Study; SQ, subsidiary question; y, year.

APPENDIX B1. EVIDENCE TABLE ON RE-SCREENING INTERVALS (SQ1)

Author, Year Quality assessment	Results	Loss to follow-up	Comments
Lindeman, 2003[42] *Fair*	Slopes of FSGs plotted over time in y for each person: 220 had a negative slope (of which 48 significantly negative [p<0.05]) and 79 had a positive slope (of which 9 significantly positive [p<0.05]) - FSGs mainly tended to < with age. 4 of 299 (1.3%) with entry FSG < 126 mg/dL and 6+ annual visits have subsequently met criteria for DM2 (2 consecutive FSGs > 126 mg/dL). Mean number of annual examinations 12.4 y (SD) 0 of 68 > 75 y old developed diabetes or significantly positive slope.	Started with 303 in 1980 (195 in this cohort lost to follow-up over the years) 1985, 56 participants added to replace those to death or drop out (# not given) 1997, 310 had returned for 6 annual visits; of which 164 had returned for 12+ annual visits 11 dropped from analysis because of diabetes diagnosis 299 in final analysis with 6+ exams; entire analysis has data over 18 y	Paper states that ADA recommends screening for everyone > 45 y every 3 y. Author's conclusion that not necessary to screen non-obese elders (excluding minorities) age >65 y with a FSG <100 mg/dL, or those age >75 y every 3 y, as recommended by the ADA. Suggestions are not made for re-screening intervals in this population.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Anand et al, 2003[50] *Not rated*	To investigate whether the addition of A1c measurement to fasting glucose improves the classification of patients with glucose intolerance compared to the use of fasting glucose alone	Multi-center Canada December 1996 - October 1998	Cross-sectional study Nondiabetic participants Construct receiver operating characteristic curves for fasting glucose and A1c measurements using the 1998 WHO diagnostic criteria as gold standard	N/A	Nondiabetic status (definition NR)	Established diabetes
Bennett et al, 2007[51] *Good*	To assess the validity of A1c as a screening tool for early detection of DM2	Multiple studies in systematic review 1994 - September 2004	Systematic review	N/A	A1c articles published in English 75g OGTT results as reference test FPG as comparison test Reference test performed in at least 80% Sensitivity and specificity data of tests available Studies had to report, or have results convertable to, DCCT-aligned A1c results	Lack of inclusion criteria

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Anand et al, 2003[50] *Not rated*	Random recruitment, clinical setting NR	Total n = 936 % male NR Ethnicity: South Asian 34% Chinese 33% European 33%	NR	FPG and A1c (low-pressure chromatography - not standardized) compared to: Gold standard criteria (WHO - all 2-h glucose values follow a 75 g glucose load): **Normal** - FPG < 126 mg/dL AND 2-h glucose < 140 mg/dL **IGT** - FPG < 126 mg/dL AND 2-h glucose 140 - 198 mg/dL **Diabetic** - FPG ≥ 126 mg/dL OR 2-h glucose ≥ 200 mg/dL 1997 ADA criteria were also applied to the population and compared to WHO criteria
Bennett et al, 2007[51] *Good*	Community volunteers Primary care referrals Hospitalized patients at high-risk for diabetes/prediabetes	Community-based studies: Range of n: 401 - 10,447 Ethnicity/nationality: Australia, Italy, United States, United Kingdom Diabetes prevalence: 6.2 - 44% Age varied widely: 13 - 92 y Hospital-based studies: Range of n: 111 - 2877 Ethnicity/nationality: Australia, Poland, Japan, Chinese, Indian, Malay, Hong Kong Diabetes prevalence: 10.7 - 21% Mean age: 43 - 56 y (excluding one study, which did not report mean)	Obesity, family history of diabetes, history of gestational diabetes, history of hypertension 1 study included patients with IGT	DCCT-aligned A1c FPG 75 g OGTT (reference standard, WHO criteria used to define diabetes)

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	**Outcomes**	**Other Results**	**Comments**
Anand et al, 2003[50] *Not rated*	Optimal cut-points for diagnosis of diabetes: A1c ≥ 5.9% (95% CI): --Sensitivity - 75.0 (64.0 - 86.0) --Specificity - 79.1 (76.4 - 81.8) --Positive LR - 3.6 (2.9-4.3) --Negative LR - 0.3 (0.2-0.5) A1c ≥ 5.9% and FPG ≥ 103 mg/dL: --Sensitivity - 71.7 (60.3-83.1) --Specificity - 95.0 (93.5-96.4) --Positive LR - 14.3 (9.6-19.0) --Negative LR - 0.3 (0.2-0.4) For the diagnosis of IGT, the receiver operating characteristic curves were nearly linear, indicating any increase in sensitivity was associated with a similar increase in false-positive rates.	Prevalence of diabetes and IGT in this population using WHO criteria: --Normal - 78.4% --IGT - 15.2% --Diabetes - 6.4% Sensitivity of ADA criteria using WHO criteria as standard: 48.3 (35.7 - 61.0)	A1c correlated with stages of glucose tolerance as defined by WHO criteria. The operating characteristics of the FPG + A1c tests varied substantially between ethnic groups. The combination of both tests was least sensitive (47.4) amongst those of European descent, but had good specificity (97.6). The test performed best amongst those of South Asian descent. The reporting of likelihood ratios allows application of these tests in populations with differing pre-test probabilities of disease. The variation between ethnic groups seen here underscores the need to interpret test results according to the characteristics of the population in which it is being applied.
Bennett et al, 2007[51] *Good*	Three optimum A1c cutpoints: 5.9% - Sensitivity 76 - 95%, Specificity 67 - 86% 6.1% - Sensitivity 78 - 81%, Specificity 79 - 84% 6.2% - Sensitivity 43 - 81%, Specificity 88 - 99% FPG: ≥ 126 mg/dL - Sensitivity 19% - 91%, Specificity 21.6 - 100% (all hospital based studies had specificities of 100%)	A1c and FPG sensitivity lower for detecting IGT	Review had fairly strict inclusion criteria. Risk for diabetes varied between populations of different included studies - most studies included populations that were at higher risk for diabetes. Comparisons between studies should be interpreted with caution given the difference in included populations.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Colagiuri et al, 2004[53] *Not rated*	Evaluate the performance characteristics of the variations of a screening protocol for the identification of people with undiagnosed diabetes, IGT, or IFG	Multi-center Australia 1999-2000	Cross-sectional study Analysis of the AusDiab study	N/A	Age > 24 y	Rural communities and those with predominant Aboriginal or Torres Strait Islander populations were excluded
Edelman et al, 2004[54] *Fair*	To determine the 3 y incidence of diabetes in an outpatient population and to determine if baseline A1c is an independent predictor of new onset diabetes.	Single center United States - VA Medical Center 1996-1998	Prospective cohort	3 y	Age 45-64 y with 1 outpatient visit between October 1996 - March 1998	Prevalent diabetes by participant self-report, prescription for hypoglycemic medication, short life-expectancy, no telephone access

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Colagiuri et al, 2004[53] *Not rated*	42 representative census districts randomly chosen and all adult residents > age 24 y were approached	Total n = 11,247 Diabetes prevalence: 7.4%, half known and half undiagnosed Total n without known diabetes: 10,508 N with one risk factor and without known diabetes: 5604 Demographics NR 38% of total population age ≥ 55 y	Age ≥ 55 Age ≥ 45 with obesity, positive family history, or HTN Age ≥ 35 and high-risk ethnicity IGT or IFG Clinical cardiovascular disease History of gestational diabetes Obese women with polycystic ovary syndrome	FPG, A1c (by high-pressure liquid chromatography), and OGTT in all people without known diabetes Assessment of risk factors for diabetes Evaluated the operating characteristics of risk factor assessment along with FPG with or without A1c measurements in detecting diabetes or IGT/IFG as defined by OGTT measurement
Edelman et al, 2004[54] *Fair*	All persons with outpatient visit during recruitment period that agreed to participate	Total n = 1253 Age: 55 y % male: 94 Ethnicity: White 69% African American 29% Other 2%	Family history diabetes 38% Overweight 43% Obese 35% HTN 53%	Baseline: A1c (high-pressure liquid chromatography) and FPG if A1c ≥ 6.0% Annual follow-up for two years: self-report of new DM diagnosis Rescreening third year: identical to baseline assessment Diabetes diagnosis either FPG > 126 mg/dL or self-report

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Colagiuri et al, 2004[53] *Not rated*	N with IGT (FPG < 126 mg/dL and 2-h OGTT ≥ 140 mg/dL) = 1372 (11%) N with IFG (FPG 110-126 mg/dL and 2-h OGTT < 140mg/dL) = 642 (5.9%) The following calculations use n = 5604 (population with 1 risk factor and without known diabetes): If FPG > 108 mg/dL, then use A1c ≥ 5.3%: --DM diagnosis - sensitivity 73.7, specificity 89.2, PPV 21.4 --IGT or IFG diagnosis - sensitivity 33.5, specificity 94.1, PPV 54.8 FPG > 108 mg/dL OR A1c ≥ 5.3%: --DM diagnosis - sensitivity 84.9, specificity 73.5, PPV 11.4 --IGT or IFG diagnosis - sensitivity 60.3, specificity 80.8, PPV 40.2	NNS to identify one new case of diabetes: 32 The risk factors of age alone, or age + one additional risk, accounted for 87% with undiagnosed diabetes History of cardiovascular disease or gestational diabetes added little	Study examined the performance characteristics of the Australian screening protocol, which includes provisions to use OGTT in persons with FPG 100-124 mg/dL. Few persons in the study were identified as being from a high-risk ethnic group.
Edelman et al, 2004[54] *Fair*	N with prevalent unrecognized DM at baseline: 56/1253 (4.5%) Person-years follow-up: 3257 Incidence of DM: 2.2/100 patient-years 80% retention of cohort at three years Annual incidence of DM according to A1c: --Normal (A1c ≤ 5.5%) - 0.8%/year --High-normal (5.6-6.0%) - 2.5%/year --Elevated (6.1-6.9%) - 7.8%/year After adjusting for baseline A1c, only baseline BMI was associated with incident diabetes. Obese persons with elevated baseline A1c had annual DM incidence of 11.4%.	Odds ratio for developing DM for each additional 5 Units BMI increase was 1.7 (95%CI - 1.4-2.1)	Mostly male population - results may be less generalizable Incidence rate of DM higher in this population than in community based setting Some cases of incident DM may have been missed because only those with A1c ≥ 6.0 were screened with FPG Though this approach may sacrifice sensitivity, those at highest risk for diabetes are likely to be identified and may be re-screened at shorter intervals

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Ellison et al, 2005[55] *Not rated*	Evaluate the performance characteristics of A1c in identifying persons with undiagnosed diabetes as defined by FPG and 2-h OGTT results	Community-based subsample of a large hepatitis B screening study which targeted non-Europeans New Zealand	Cross-sectional	N/A	Participants in hepatitis B screening study age > 20 y, without known diabetes, and with A1c levels 5-7% who lived within 1 hour of testing centers	Established diabetes
Geberhiwot et al, 2005[56] *Not rated*	To determine whether A1c may be useful in selecting persons with DM risk factors for OGTT who have normal FPG levels	Single center United Kingdom	Cross-sectional	N/A	2+ diabetes risk factors Initial FPG ≤ 108 mg/dL	Established diabetes

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Ellison et al, 2005[55] *Not rated*	Community recruitment	Total n (hepatitis B screening study): 50,819 244/300 (81%) approached to participate in substudy completed all testing Age: 48.7 y % male: 50 Ethnicity: Maori 82% Pacific Islander 7% Asian 9% European 4%	Most of population from high-risk ethnic group, other risk factors NR	A1c (high-pressure liquid chromatography), OGTT
Geberhiwot et al, 2005[56] *Not rated*	Convenience sample of metabolic clinic referral population	Total n = 580 Study n (initial FPG ≤ 108 mg/dL) = 225 Age: Men 52.9 y (12.0) Women 53.3 y (13.5) % male: 52 Race NR	Obesity, dyslipidemia, HTN, previous history of IGT, family history of diabetes	A1c (high-pressure liquid chromatography), OGTT Diabetes diagnosis: WHO criteria according to OGTT results

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Ellison et al, 2005[55] *Not rated*	Of total n (50,819), mean (SD) A1c was 5.4 (1.0). Diabetes substudy: 12% had A1c ≥ 6.1%, 4% had A1c ≥ 7.1% Prevalence of undiagnosed diabetes (as defined by FPG ≥ 126 mg/dL or 2-h OGTT ≥ 200 mg/dL): 35/244 = 14.3% Ability of A1c ≥ 6.1% to detect: FPG ≥ 126 mg/dL: Sensitivity - 94% Specificity - 77% FPG ≥ 110 mg/dL: Sensitivity - 64% Specificity - 89% 2-h OGTT ≥ 200 mg/dL: Sensitivity - 90% Specificity 73%	The receiver operating characteristics are presented and the greatest specificity for detecting diabetes by elevated FPG comes with A1c cutoff of 6.4% (sensitivity 59%, specificity 93%).	The population under study is mostly comprised of ethnicity groups at high risk for diabetes and the prevalence of undiagnosed diabetes in this population is high. Those with A1c < 5% were excluded from study, so the persons at lowest risk for having undiagnosed diabetes were not represented in this study.
Geberhiwot et al, 2005[56] *Not rated*	Prevalence rates: --Normal glucose tolerance - 173/225 = 76.9% --IGT - 45/225 = 20% --DM - 7/225 = 3.1% From receiver operating characteristic curve, optimal A1c cut-point of 5.6% in detecting 2-h OGTT ≥ 140 mg/dL: --Sensitivity - 72% --Specificity - 77%	Mean FPG (SD): 97 mg/dL (9 mg/dL)	Almost one-quarter of this population with normal FPG had abnormal glucose tolerance on OGTT testing. This is a referral population at risk for diabetes, so generalizability may be an issue. Not clear how many persons would fall into lowered threshold for IFG diagnosis (100 mg/dL)

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Jesudason et al, 2003[57] *Not rated*	1) Compare different thresholds of A1c and FPG to OGTT for screening DM2 2) Determine relationship between A1c and FPG and cardiovascular risk 3) Compare A1c measured by a portable device to HPLC	Single center United Kingdom	Cross-sectional	N/A	Age > 18 y with no prior history of diagnosed diabetes and with risk factors for DM2, or symptoms of hyperglycemia	Pregnant women
Maynard et al, 2007[58] *Not rated*	Compare the ability of Spectral measurement of AGEs (SAGE) to detect undiagnosed diabetes and IGT to FPG and A1c	Single center United States	Cross-sectional	N/A	Age > 18 with no prior diagnosis of diabetes, with 1+ ADA diabetes risk factors, and found to have abnormal glucose tolerance (IGT or diabetes) according to OGTT results	Established diabetes
McAulley et al, 2004[59] *Not rated*	Assess acceptability, sensitivity, specificity, effectiveness, and cost of A1c measured by rapid immunoassay (A1c analyzer: DLA 2000)	Single center Australia Aboriginal population 1999	Cross-sectional	N/A	Aboriginal above age 30 and with no history of diabetes	NR

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Jesudason et al, 2003[57] *Not rated*	Volunteers from community	N = 505	Obesity, family history of diabetes, history of gestational diabetes	A1c (by HPLC and DCA 2000, a portable immunoassay device from Bayer) Fasting plasma glucose 75g OGTT Questionnaire re: existing CV disease
Maynard et al, 2007[58] *Not rated*	Volunteers from community	Total n = 351 N with abnormal glucose tolerance = 84	Many from high-risk ethnic group, other factors NR	SAGE FPG OGTT A1c (HPLC)
McAulley et al, 2004[59] *Not rated*	Consecutive patients January - May 1999	N = 238	NR	A1c by DCA 2000 (immunoassay) FPG 75gm OGTT All patients with A1c over 7% were referred for OGTT Patients with A1c 6-7% were referred for OGTT if they had risk factors for diabetes

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Jesudason et al, 2003[57] *Not rated*	Prevalence rates: WHO criteria --IGT - 123/505 = 24.4% --DM - 54/505 = 10.7% ADA criteria --IFG - 36/505 = 7.1% --DM - 20/505 = 4.0% A1c (HPLC assay) compared to OGTT: ≥ 4.7% - Sensitivity 100%, Specificity 10.0%, CV risk ratio 1.3 ≥ 5.6% - Sensitivity 85.2%, Specificity 80.5%, CV risk ratio 1.8 ≥ 6.2% - Sensitivity 42.6%, Specificity 99.1%, CV risk ratio 2.3 FPG (mmol/L) compared to OGTT: ≥ 4.7 - Sensitivity 100%, Specificity 23.1%, CV risk ratio 1.4 ≥ 5.6 - Sensitivity 79.6%, Specificity 85.8%, CV risk ratio 1.7 ≥ 6.4 - Sensitivity 59.3%, Specificity 99.1%, CV risk ratio 2.0 A1c by HPLC compared to DCA2000 assay: good correlation - R2 0.876	N/A	Did not find independent association between A1c and CV risk - both FPG and A1c were continuously associated with increasing CV risk.
Maynard et al, 2007[58] *Not rated*	IGT - 55/351 = 15.7% Undiagnosed DM2 - 29/351 = 8.3% A1c ≥ 5.8% - Sensitivity 63.8%, Specificity 77.4% FPG ≥ 100 mg/dL - Sensitivity 58.0%, Specificity 77.4% SAGE ≥ 50 - Sensitivity 74.7%, Specificity 77.4%	Area under the curve: A1c - 79.2% Area under the curve: FPG 72.1% Area under the curve: SAGE 79.7%	Paper mainly focused on SAGE operating characteristics. A1c had slightly better sensitivity at a given specificity compared to FPG.
McAulley et al, 2004[59] *Not rated*	Mean A1c: 5.4% Only 46/238 had A1c >6% and only 14 of these had OGTT performed	N/A	Poor quality study. Few people had enough data available to compare A1c and other methods of screening. Few conclusions can be drawn from the study.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Norberg et al, 2006[60] *Fair*	1) To find a simple and practical method to identify persons at high risk for future DM2 2) Compare operating characteristics of new and old FPG criteria in screening models of future DM2	Community/Primary care centers Sweden 1989 - 2001	Population-based prospective cohort study matching incident diabetes cases to non-diabetic referents	8.8 y (mean)	Incident diabetes according to WHO criteria	Unavailability of blood samples
Perry et al, 2001[52] *Not rated*	To find more sensitive criteria, in a population at-risk for diabetes and with nondiagnostic FPG, to diagnose people with IGT or diabetes as diagnosed by OGTT	Part of the EDIP study Multi-center study in the United States	Cross-sectional analysis of the EDIP study, which is a randomized-controlled trial	N/A	Risk-factors for diabetes and FPG 100-144 mg/dL	Age < 24, pregnancy, recent cancer treatment, HIV or tuberculosis, recent myocardial infarction/bypass grafting/angioplasty, congestive heart failure, 3rd degree atrioventricular block, uncontrolled HTN, elevated AST/ALT, serum creatinine > 2.2 mg/dL in men and 2.1 in women, anemia, hypertriglyceridemia

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Norberg et al, 2006[60] *Fair*	Population-based cohort from 1 county in northern Sweden 52% of population participated in survey and outcomes tracked through local hospital and primary care centers	Total n = 28,736 Prevalent diabetes: 6088 Incident diabetes: 277 Final n = 164 cases and 304 referents (after exclusion of type 1 diabetes and persons without blood samples)	NR	75g OGTT FPG A1c (by HPLC)
Perry et al, 2001[52] *Not rated*	Volunteers from community	N = 244 Age: 53.6 y (11.4) % male: 32 Ethnicity: Caucasian 78% African-American 18% Hispanic 2% Asian 2%	Obesity, history of gestational diabetes, family history of diabetes, patient report of "pre-diabetes"	Comparison of FPG and A1c (immunoturbidimetric immunoassay) with 2-h 75g OGTT values

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Norberg et al, 2006[60] *Fair*	Background prevalence of DM2: 5.2% From multivariate prediction model, the following were predictors of DM2 development: A1c ≥ 4.7%*, BMI ≥ 30, IFG (by WHO criteria), and IGT (in women). Using model of IFG or IGT, BMI ≥ 27, A1c ≥ 4.7%: - 2 of 3 criteria - PPV 17-27%, NPV 98-99.5% - 1 of 3 criteria - PPV 8 - 9%, NPV 98-99.5%, proportion of attributable cases = 82-92% Family History + BMI ≥ 30 + A1c ≥ 4.7%: PPV 35%	Adding OGTT identified few additional persons FPG cutoff of 5.6 mmol/l (new criteria) decreased PPV without clear increase in proportion of subjects at risk	OGTT adds little to prediction of future DM2 over and above the suggested model. The PPV were modest at best, but the high NPV may be of use in identifying patients who could potentially forego regular screening. The participation rate of only about 50% may be a limitation, though characteristics between participants and non-participants were similar.
Perry et al, 2001[52] *Not rated*	121/244 (50%) participants had diabetes as defined by 2-h OGTT values ≥ 200 mg/dL Elevated A1c (> 2 standard deviations above mean): --Sensitivity 61% (95% CI: 51-71) FPG > 126 mg/dL: --Sensitivity 45% (35-55) Combination of FPG > 126 mg/dL and elevated A1c: --Sensitivity 76% (66-86) Two FPG measures > 126 mg/dL: --Sensitivity 42% (32-52)	N/A	Specificities (or data to derive them) are not reported. Of note, 50% of those with diabetes risk factors and FPG in the IFG range had diabetes by 2-h OGTT.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Peters et al, 1996[61] *Fair*	To determine if A1c could be used in place of OGTT to diagnose diabetes	Multiple studies in systematic review Search 1966 - 1994	Systematic review	N/A	Reports in which A1c were measured concurrently with and compared to OGTT	Study populations who had conditions that would alter glucose tolerance (pregnancy, cystic fibrosis)
Rohlfing et al, 2000[62] *Not rated*	To determine the sensitivity and specificity of A1c in diagnosing diabetes as defined by FPG ≥ 126 mg/dL	Multicenter/Population based - NHANES III United States 1988-1994	Cross-sectional	N/A	NHANES participants with fasting plasma glucose age ≥ 20 y	Nonfasting status, prevalent diabetes by patient report
Shibata et al, 2005[63] *Not rated*	To compare A1c and FPG in their ability to detect post-prandial hyperglycemia	Single center, primary care Japan 2001-2002	Cross-sectional	N/A	All individuals undergoing routine medical checkup at study center Only persons with discordant FPG and A1c measures underwent OGTT testing and were included in analysis FPG cutoff - 7.0 mmol/L A1c cutoff - 6.5%	Prevalent diabetes (those on diabetes treatment)

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Peters et al, 1996[61] *Fair*	MEDLINE search of English language abstracts, reference list searches and expert files	Total number studies = 34 18/34 studies provided individual level data giving sample of 11,276 subjects (83% of all subjects in literature) Final analysis used data from 10 studies, in which an A1c assay was used (the other glycosylated hemoglobin assays had greater variance): 8984 subjects	NR	FPG A1c (method not defined) 75g OGTT
Rohlfing et al, 2000[62] *Not rated*	Population-based survey with oversampling of non-Hispanic blacks and Mexican-Americans	Total n = 6559 Non-Hispanic white 2789 Non-Hispanic black 1752 Mexican-American 1751 Other 267	NR	FPG A1c (by HPLC) 2871/6559 underwent OGTT
Shibata et al, 2005[63] *Not rated*	Population- based, consecutive enrollment	Total n = 6184 Those included in analysis including OGTT n = 104	Mean BMI: Men 22.9 (2.8) Women 22.1 (2.9)	FPG A1c (by HPLC) 75g OGTT (for those with discordant FPG and A1c results)

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Peters et al, 1996[61] *Fair*	Sensitivity/specificity/predictive value positive of A1c in detecting OGTT > 200 mg/dL in hypothetical population with diabetes prevalence of 6%: A1c + 2 SDs 66%/98%/63% A1c + 3 SDs 48%/100%/90% In normoglycemic patients, 69.1% had A1c < 5.5%, 90.9% had A1c < 6.0% Sensitivity/Specificity for clearly diabetic and clearly normal cases: A1c 5.5% - Sensitivity 100.0%, Specificity 69.1% A1c 7.0% - Sensitivity 99.6%, Specificity 99.9% Using A1c cutoff of 7%, false positive rate of only 0.1% (normal glucose tolerance), but 58% false negative rate	Prevalence of diabetes: 6.5% Mean A1c (SD) in patients with normoglycemia (FPG < 115 mg/dL) and OGTT < 140 mg/dL: 5.2 (0.6) In patients with normoglycemia and OGTT > 200 mg/dL: 5.8 (1.0)	Authors argue that, in a population at high-risk for diabetes, A1c > 7% is an appropriate cut-off. It will miss many patients with abnormal OGTT, but since A1c is used to guide clinical treatment, the cut-point of 7% would identify the population most likely to require pharmacologic intervention, while others would benefit from lifestyle modification.
Rohlfing et al, 2000[62] *Not rated*	Sensitivity%/Specificity% at different A1c cutoffs (FPG ≥ 126 mg/dL is gold standard): A1c 5.6 (1SD above mean) - 83.4/84.4 6.1 (2 SD above mean) - 63.2/97.4 (non-Hispanic black: 75.8/93.0, Mexican-American: 83.6/97.8) 6.5 (3 SD above mean) - 42.8/99.6 7.0 (4 SD above mean) - 28.3/99.9	Prevalence of undiagnosed diabetes (FPG ≥ 126 mg/dL): 4.0% Mean A1c (SD) for normoglycemic participants: 5.17 (0.45)	A1c had higher sensitivity in high-risk ethnic groups. The use of FPG as the gold standard in this case is of some concern given that the sensitivity of this test has been called into question when compared to OGTT results.
Shibata et al, 2005[63] *Not rated*	Participants with post-prandial hyperglycemia - 77 54/77 had FPG > 7.0 mmol/L, but A1c < 6.5% true-positive odds ratio of A1c to FPG was 0.43 (0.26-0.69)	Reducing A1c cutoff improved detection of persons with post-prandial hyperglycemia. False-positive OR A1c/FPG 0.40 (0.13 - 1.27), p = 0.090	Cutoffs chosen were fairly high. Clearly, lowering A1c cutoff will improve sensitivity. Low rate of false positives in study limit interpretation of comparative false positive rates between both tests.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Study objective	Setting; Country	Study design	Length of follow-up	Inclusion criteria	Exclusion criteria
Simmons et al, 2005[64] *Not rated*	To compare A1c, FPG and risk factors in their ability to detect abnormal glucose tolerance	Community-based New Zealand	Cross-sectional	N/A	Persons without known diabetes	Known diabetes
Wang et al, 2002[65] *Not rated*	To find the optimal combination of A1c and FPG for detecting diabetes as defined by 2h OGTT results in participants with IFG	Multiple communities United States	Cross-sectional and prospective cohort (though essentially was 2 cross-sectional studies)	4 y	Age 45-74 y American Indian A1c, FPG, and OGTT measures available	Prior diabetes, oral hypoglycemic or insulin use, renal dialysis, history of kidney transplant

*A1c in this study was calibrated according to Swedish MonoS standard and values are approx 1% lower than DCCT calibration

Abbreviations: ADA, American Diabetes Association; ALT, Alanine AminoTransferase; AST, Aspartate AminoTransferase; BMI, body mass index; CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; DM, diabetes; DM2, type 2 diabetes; EDIP, Early Diabetes Intervention Program; FPG, fasting plasma glucose; h, hour; HIV, Human Immunodeficiency Virus; HPLC, high-performance liquid chromatography; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LR, likelihood ratio; N, number of participants in study; N/A, not applicable; NHANES, National Health and Nutrition Examination Survey; NPV, negative predictive value; NR, not reported; OGTT, oral glucose tolerance test; PPV, positive predictive value; ROC, receiver operating curve; SAGE, Spectroscopic measurement of advanced glycation end products; SD, standard deviation; SQ, subsidiary question; WHO, World Health Organization; y, years.

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Participant selection	Population	Diabetes risk factors	Screening intervention
Simmons et al, 2005[64] *Not rated*	Population-based sampling within European, Maori, and Pacific Islander areas, stratified by age and ethnicity	Total n screened for diabetes = 1899 OGTT performed, n = 534 (67.9% of those invited)	Among those with new diabetes: Mean age 55 y (9) Obesity 79.1% Family history 33.7% HTN treatment 18.5%	All patients - random glucose Those with random glucose ≥ 117 mg/dL within 2 h of a meal, or ≥ 108 mg/dL 2 h after a meal, were invited for OGTT at which time FPG and A1c (immunoturbidmetric assay) was performed. A random sample (28%) of those with normoglycemia at initial screening were also selected for OGTT.
Wang et al, 2002[65] *Not rated*	Population-based recruitment	Baseline exam n = 2389 Second exam n = 1644	NR	FPG A1c (by HPLC) 75g OGTT

APPENDIX B2. EVIDENCE TABLE ON A1C (SQ2)

Author, Year *Quality*	Outcomes	Other Results	Comments
Simmons et al, 2005[64] *Not rated*	Sensitivity = specificity for diagnosis of diabetes at following cutpoints: A1c 5.6% Random glucose 104 mg/dL Fasting glucose 104 mg/dL Number of risk factors 1 ROC at these cutpoints: A1c 0.86 (0.82 - 0.90) Random glucose 0.75 (0.69 - 0.80) Fasting glucose 0.92 (0.89 - 0.95)* Number of risk factors 0.60 (0.55 - 0.66) * $p < 0.0083$ vs A1c	ROC improved for all measures in higher risk ethnic subgroups (Pacific Islander > Maori > European)	Gold standard of OGTT applied to less than half original sample. Data presented cannot be used to calculate sensitivity and specificity.
Wang et al, 2002[65] *Not rated*	FPG ≥ 126 mg/dL sensitivity 44.8 - 62.8% To detect new diabetes amongst IFG participants: - FPG + A1c had largest area under ROC curve (0.72 vs 0.64 with FPG alone, $p < 0.001$) Optimal critical line: sensitivity 58.8%, specificity 76.8% for following situations - A1c 6.5 when FPG = 110 A1c 4.6 when FPG = 126 FPG 162.9 when A1c 0	Approximately 20% (19.3% baseline and 22.9% at second test) of IFG participants had 2 h OGTT > 200mg/dL (false negatives)	

APPENDIX B3. SCREENING EVIDENCE TABLE (KQ1)

Author, Year Quality rating	Study objective	Country; Setting	Study design	Length of follow-up	Inclusion criteria	Outcomes	Adherence Withdrawals (%)	Conclusions	Comments
Agarwal et al, 2006[86] *Poor*	To compare the occurrence of diabetic retinopathy in targeted screening diabetic patients with newly-diagnosed diabetic patients in general practice	India, rural communities and urban clinics	Cross-sectional with comparison group	NA	Group I (targeted diabetes screening): N=173; >30 years who attended rural or urban diabetes screening clinics, who screened (+) for DM2, and who then reported for eye examination Group II (newly diagnosed in general practice): N=128; diagnosed with DM in last 1 month and reported for eye examination	Diagnosis of diabetic retinopathy: Group I: 6.4% Group II: 11.7% (between-group p-value =0.22)	NA	Diabetic retinopathy was found in both screen-detected and newly-diagnosed in general practice, with no significant difference in prevalence between the 2 groups.	Group I: only 15% reported for eye examination; 100% for Group II Study performed in urban and rural India; may not be applicable to United States populations
Olafsdottir et al, 2007[85] *Fair*	To establish a gold standard for prevention of blindness in DM2 populations by comparing a DM-screened population to a nonDM population for visual acuity	Sweden, using national register for diabetes and control group from population register	Cohort with comparison group	NA	All inhabitants of Laxa with DM2; this community has a systematic screening program Age- and sex-matched controls from national register	No significant difference in visual acuity between DM and control groups; except more control subjects had acuity ≥ 1.0 (p=0.027)	NA	In a population that had been screened for DM2 and for diabetic eye disease, the prevalence of visual impairment and blindness was no greater than in the control group	DM group was considered 'screened' but likely some were detected clinically
Schellhase et al, 2003[84] *Good*	To determine if glucose screening reduces the risk of diabetic complications	United States, HMO	Case control	10 y	Cases: diagnosed with DM2 after age 3y, had developed 1+ microvascular complications attributable to DM2, enrolled in health plan for 10+y Control subjects: randomly selected and matched to cases Exclusion criteria NR	Number of screening BG tests over 10y period: cases 6.3, controls 4.8 88% of testing was random BG; 81% of BG tests occurred without symptoms (i.e. were screened) OR for BG screening at least once vs no screening: (adjusted) 0.87 (0.38-1.98)	NA	Persons who had 1+ screening events in the 10y period had a 13% decreased the risk of developing severe microvascular complications from DM2 after adjusting for multiple confounding factors	The study included persons tested without symptoms of diabetes, persons with HTN, or other incidental screening with other chronic illnesses that could include CVD

Abbreviations: BG, blood glucose; CVD, cardiovascular disease; DM, diabetes; DM2, type 2 diabetes; HMO, Health Maintenance Organization; HTN, hypertension; N, number of participants, NA, not applicable; NR, not reported; OR, odds ratio; y, years.

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Study aims	Country	Treatment groups sample size	Length of follow-up	Inclusion criteria
KQ1					
ADDITION Study by Lauritzen et al, 2000[88] *(Anglo-Danish Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care)*	1) Evaluate whether screening for prevalent undiagnosed diabetes is feasible 2) Evaluate whether subsequent optimized intensive treatment and associated risk is feasible and beneficial	Multi-center: Denmark, England, Netherlands	Goal = 1,500 conventional treatment vs. 1,500 intensive treatment	5 y	Screening study: Ages 40-69 Without known diabetes Treatment study: Newly diagnosed DM2 (FPG ≥ 108 or 2-h > 198 mg/dl [≥ 6.0 or 2-h OGTT >11.0 mmol/l]
KQ2					
ACCORD Trial[102] *(Action to Control Cardiovascular Risk in Diabetes Trial)* Sponsored by National Heart, Lung, and Blood Institute (NHLBI)	1) Using intensive glycemic control, intensive blood pressure control, and intensive lipid management to prevent major cardiovascular events in adults with DM2	Multi-center: Canada and United States (77 clinics)	Goal: 10,000 (5,000 I; 5,000 C)	4-8 y	DM2 diagnosis for >3 months Aged 40 y or older: history of CVD* Aged 55 y or older: a history of CVD or at high risk for experiencing a CVD event *Heart attack, stroke, history of coronary revascularization, history of peripheral or carotid revascularization, or demonstrated angina

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Exclusion criteria	Participant selection	Diabetes Treatment
KQ1			
ADDITION Study by Lauritzen et al, 2000[88] *(Anglo-Danish Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care)*	Screening study: Previously diagnosed diabetes Treated with blood glucose lowering agents Treatment study: IGT and/or IFG, contraindications or intolerance to study medications, alcoholism, drug abuse, psychosis or emotional problems, malignant disease with a poor prognosis, pregnant or lactating	Population-based screening recruitment in outpatient clinics	Stepwise increases in drug treatment for hyperglycemia (drugs not specified)
KQ2			
ACCORD Trial[102] *(Action to Control Cardiovascular Risk in Diabetes Trial)* Sponsored by National Heart, Lung, and Blood Institute (NHLBI)	Age <40 or >79 Hypoglycemic coma/seizure within last 12 months Hypoglycemia requiring 3rd party assistance in last 3 months with concomitant glucose < 60 mg/dl (3.3 mmol/l) History consistent with type 1 diabetes Unwilling to do frequent capillary blood glucose self-monitoring or unwilling to inject insulin several times a day BMI > 45 kg/m2 Serum Creatinine > 1.5 mg/dl (132.6 umol/l) obtained within the previous 2 months Transaminase >2 times upper limit of normal or active liver disease ongoing medical therapy with known adverse interactions with the glycemic interventions (e.g., corticosteroids, protease inhibitors) Cardiovascular event or procedure (as defined for study entry) or hospitalization for unstable angina within last 3 months Current symptomatic heart failure, history of NYHA Class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25% A medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 y Any factors likely to limit adherence to interventions Failure to obtain informed consent from participant Currently participating in another clinical trial Any organ transplant Weight loss > 10% in last 6 months Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practicing birth control Participants with recurrent requirements for phlebotomy or transfusion of red blood cells	Population-based screening recruitment in outpatient clinics	Hypoglycemic agents, hydroxymethylglutaryl-CoA reductase inhibitors, and antihypertensive agents

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Intervention
KQ1	
ADDITION Study by Lauritzen et al, 2000[88] *(Anglo-Danish Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care)*	2 phases: Screening study to assess 3 approaches to identifying undiagnosed diabetes: *Denmark*: questionnaire to assess risk factors sent to patients, encouraging those with high risk to contact physician for screening test; *England*: validated risk score generated from computerized medical records used to determine high risk; *Netherlands*: all age-qualified patients will be offered screening test. Random capillary blood glucose measured using HemoCue. If ≥ 99 mg/dl (5.5 mmol/l), then fasting glucose test and OGTT Treatment study: Conventional care (national guidelines) vs. intensive, multifactor care (lifestyle advice, aspirin and ACE-inhibitors, protocol-driven tight control of blood glucose, blood pressure, and cholesterol, lifestyle changes) Further randomization will allocate some patients to country-specific interventions with emphasis on adherence to lifestyle changes and medication.
KQ2	
ACCORD Trial[102] (*Action to Control Cardiovascular Risk in Diabetes Trial)* Sponsored by National Heart, Lung, and Blood Institute (NHLBI)	All participants receive drug treatment to lower blood glucose to either current guideline targets, or more aggressive targets (N=10,000) Depending on blood pressure and cholesterol levels, participants are further assigned to receive high blood pressure or high blood fats (cholesterol and triglycerides) drug treatment, at either current guideline targets, or more aggressive targets

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Primary endpoint (s)
KQ1	
ADDITION Study by Lauritzen et al, 2000[88] *(Anglo-Danish Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care)*	Primary: All cause mortality, cardiovascular mortality/morbidity, nonfatal myocardial infarction, nonfatal stroke, amputations, hospitalization for angina or congestive heart failure, coronary revascularization, or peripheral revascularization Secondary: Renal impairment, blindness, diabetic ulcers, retinopathy, reduced visual acuity, macular edema, health status and utility, quality of life, satisfaction, costs Intermediate: Smoking status, physical activity, lipid levels, blood pressure, microalbuminuria, BMI, etc Process-of-care: Visits to outpatient clinics, outpatient admissions
KQ2	
ACCORD Trial[102] *(Action to Control Cardiovascular Risk in Diabetes Trial)* Sponsored by National Heart, Lung, and Blood Institute (NHLBI)	Primary: First occurrence of a major CVD event, specifically nonfatal heart attack, nonfatal stroke, or cardiovascular death

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Study aims	Country	Treatment groups sample size	Length of follow-up	Inclusion criteria
KQ3					
CANOE Trial Zinman et al, 2007[166], 2006[167] (*Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) Trial)*	1) To determine whether treatment with metformin plus rosiglitazone, in addition to a healthy living lifestyle programme in people with IGT, will prevent development of DM2 2) To determine whether this treatment approach will improve cardiovascular risk factors associated with IGT	Canada, multicenter	Goal = 200 total (100 I; 100 C)	3-5 y	IGT diagnosis Ages 30-75 y (18-75 for Native Canadians) Resident of Ontario
FIN-D2D Study by Saaristo et al, 2007[168] (*National type 2 diabetes prevention programme in Finland)*	1) To reduce the incidence and prevalence of DM2 and prevalence of cardiovascular risk factor levels using lifestyle interventions 2) To identify individuals who are unaware of their DM2 3) To generate regional and local models and programs to prevent DM2 4) To evaluate effectiveness, feasibility, and costs of the programme 5) To increase the awareness of DM2 and it's risk factors	Finland (5 hospital districts)	Potential population of 1.5 million	4 y	Population-wide

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; C, control (placebo) group; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; FPG, fasting plasma glucose; h, hour; I, intervention group; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; KQ, key question; LFT, liver function test; N, number of participants in study; NYHA, New York Heart Association; OGTT, oral glucose tolerance test; y, years.

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Exclusion criteria	Participant selection	Diabetes Treatment
KQ3			
CANOE Trial Zinman et al, 2007[166], 2006[167] (*Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) Trial)*	Current use of metformin or rosiglitazone Prior use of medication to treat DM2 (except gestational DM2) Use of drugs known to exacerbate glucose tolerance History of DM2 (except gestational DM2) Clinically significant hepatic disease, LFTs > 2.5 times the upper limit of normal, or renal dysfunction Active liver disease including jaundice, chronic hepatitis or previous liver transplant Anemia Any major illness with life expectancy <5 y or that may interfere with study participation Involvement in another drug study History of congestive heart failure or current congestive heart failure Excessive alcohol consumption Pregnancy or unwilling to use reliable contraception Inability to communicate in English language	Recruitment detail NR	Pharmacotherapy and healthy lifestyle counseling
FIN-D2D Study by Saaristo et al, 2007[168] (*National type 2 diabetes prevention programme in Finland)*	Population-wide	Population-based screening recruitment in hospitals	Pharmacotherapy, tailored dietary and exercise goals, & group guidance maintenance sessions.

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Intervention
KQ3	
CANOE Trial Zinman et al, 2007[166], 2006[167] (*Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) Trial)*	Metformin (500 mg) plus rosiglitazone (2 mg) administered as one capsule twice daily, will be compared to matched placebo. In addition, a healthy living lifestyle programme based on latest national evidence-based guidelines recommended by Canadian Diabetes Association (includes discussions of diabetes prevention, physical activity, nutrition, weight loss, and maintenance of a healthier lifestyle), will occur in both treatment and control groups
FIN-D2D Study by Saaristo et al, 2007[168] (*National type 2 diabetes prevention programme in Finland)*	3 Strategies: High-risk identification strategy: Uses "FINDRISC" the Finnish Diabetes Risk Score calculator to determine risk level. Scores < 7 are not at risk & do not receive preventive measures. Scores 7-14 receive written info on preventive measures. Scores ≥ 15 receive OGTT & appropriate treatment measures (see next strategy for details). Early diagnosis and management: To bring those newly diagnosed with DM2, using the FINDRISC score calculator, into immediate treatment, with the goal of preventing diabetic complications. Treatment includes pharmacotherapy, tailored dietary and exercise goals, & group guidance maintenance sessions. Population strategy: Media communication, training, life-style counseling (physical and nutrition); an extensive network to support these activities will be used. All will be evaluated (feasibility, cost effectiveness, effects) by Finnish National Public Health Institute.

APPENDIX B4. EVIDENCE TABLE OF ONGOING TRIALS

Trial; Author, Year	Primary endpoint (s)
KQ3	
CANOE Trial Zinman et al, 2007[166], 2006[167] (*Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) Trial)*	Primary: Development of new-onset diabetes Secondary: Longitudinal changes in blood pressure, microalbuminuria, lipids, beta cell function, insulin resistance, inflammatory marker C-reactive protein, homocysteine, adiponectin, insulin and proinsulin, & assessment of lifestyle intervention
FIN-D2D Study by Saaristo et al, 2007[168] (*National type 2 diabetes prevention programme in Finland)*	DM2 diagnosis, incidence rates, feasibility, cost effectiveness, & effects of program

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	Objective	Type of screening; Perspective	Type of model	Population; Country	Included costs	Discount rate
CDC Diabetes Cost-effectiveness Group, 1998[90]	To estimate the cost-effectiveness of early detection and treatment of DM2 compared to current practice (clinical diagnosis)	One-time opportunistic screening during regular physician visit; Single-payer health care system	Monte Carlo Computer simulation	Hypothetical cohort of 10,000 persons with newly-diagnosed DM2 from the general United States population >25 y	Direct costs: screening, diagnostic tests, treatment	3%; costs expressed in in 1995 US$
Goyder et al, 2000[91]	To determine whether the potential benefits of screening are likely to outweigh the potential harms; explore which variables influence the balance of benefit and harm from screening	Universal screening Perspective: NA (does not involve cost)	Decision analysis	Cohort of 10,000, mainly Caucasian 45-60 y United Kingdom	NA	3% annual rate for QALYs
Hofer et al, 2000[92]	To define the relative benefits of screening for DM2	Universal and targeted screening	Markov model	Cohort of recent onset DM2 (<5y)	NA	NA
Chen et al, 2001[43]	To evaluate the efficacy of screening for DM2 compared to no screening; to evaluate the inter-screening interval and age of start of screening on health outcomes; to examine the CE of screening	Mass screening Single payer health plan	Markov process Monte Carlo simulation	Over age 30y, general community population; cohort of 30,000 Taiwan	Direct costs including costs of screening, treatment; indirect costs not included; costs in US$	3% annual rate

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	Base case assumptions	Time horizon	Data sources	Sensitivity analyses	Intervention
CDC Diabetes Cost-effectiveness Group, 1998[90]	Screening reduces the prediagnosis interval by 5y (from 10.5y to 5.5y); prevalence of undiagnosed DM2 is 3.2% (varied by age, sex, race per NHANES data); glycemic control relates to microvascular (but not macrovascular) complications	Lifetime or age 95y	Various epidemiologic data and treatment trials, including UKPDS	A1c as screening test (decreases $/QALY), sensitivity and specificity of the screening test, prediagnosis interval (shorter interval, increased $/QALY); prevalence of DM2 (increased prevalence produces decreased $/QALY); intensive treatment for glycemic control (increases $/QALY)	One-time screening intervention with FPG, OGTT for confirmation of positives
Goyder et al, 2000[91]	Positive screening test is followed by a 'gold standard' diagnostic test before treatment; harms of negative or false positive test negligible; reduction in QALYs associated with early diagnosis proportional to time from diagnosis to when clinical diagnosis would have been made; optimal treatment is available from the time of clinical diagnosis; diabetes will be diagnosed at the time of or before symptomatic complications present; baseline risk of CVD complications is similar in diagnosed and undiagnosed DM2; sensitivity of screening test 90%; treatment for 1 CVD risk factor leads to a risk reduction of 1/3; extent to which BG is reduced during early treatment is 50% of that achieved after clinical diagnosis; clinical diagnosis 6y after onset	Lifetime	UKPDS and other sources	One-way sensitivity analysis: benefits no longer outweigh harms if: baseline annual risk of CVD is <0.8%; RR CVD is reduced by <13% during earlier treatment; discount rate >7%	Various interventions for hyperglycemia, HTN, lipids
Hofer et al, 2000[92]	Onset of DM2 prior to diagnosis 5y; A1c increases at constant rate of 0.2%/y in diagnosed and undiagnosed; one-time drop in A1c of 10% at time of start of treatment; undiagnosed were diagnosed at rate of 5%/y up to A1c of 13%, beyond which were diagnosed at 50%/y	Lifetime	NHANES III, UKPDS for progression of glycemia, DCCT for benefits of tight glycemia control on ESRD and retinopathy	Duration undiagnosed DM2, treatment effect, rate of case finding	Perfect screening: diagnosis at time of onset Improved treatment: A1c $\leq$ 9%
Chen et al, 2001[43]	Early diagnosis and treatment can control BG and reduce micro- and macrovascular complications	30y or until death	Taiwan demographic data; transition parameters from a variety of sources including Framingham Heart Study, UKPDS	None	Screening program lasts for 10y; standard treatments such as that of UKPDS for persons with DM2

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	Outcomes	Conclusions	Quality assessment
CDC Diabetes Cost-effectiveness Group, 1998[90]	Incremental cost of screening is $236,449 per life-year gained and $56,649/QALY; more CE among younger persons (as more complication-free years and CHD not modeled) and among African Americans	Screening may produce cost/QALY within range of currently acceptable, especially for younger persons and African Americans	Limited sensitivity analyses CVD not modeled; screening and treatment only influence microvascular complications No information on how QALYs determined No mention harms of screening Lack of transparency of details of model Used data from DM1 for microvascular disease risk reduction with treatment
Goyder et al, 2000[91]	QALYs gained by screening 10,000 persons: 10.5: 4 from postponed microvascular complications, 17 from avoided CVD complications and 11 lost from early diagnosis	The immediate disutility of earlier diagnosis and additional treatment may be greater than the potential long-term benefit from postponing microvascular complications; screening decisions should be based largely on CVD risk and interventions to reduce that risk	Used data from DM1 for microvascular disease risk reduction with treatment Details and assumptions of the model not clear
Hofer et al, 2000[92]	Number blind/1000 persons with diabetes, age 40y, A1c 12%: Case finding: 141 Perfect screening: 133 Case finding, A1c <9%: 90 Screening, A1c <9%: 41 Screening produces 7% of the benefit of reduced number of cases of blindness; improved treatment alone is 65% Targeted screening (with 2+ risk factors): achieved 75% of the benefits of universal screening	Largest impact of improving treatment and diagnosis is in younger person with high A1c; focus should first be on improving glycemic control of known diabetics with high A1c; if that is achieved then the benefits of screening will become more important	Does not include benefits of HTN and lipid treatment Only examines microvascular complications
Chen et al, 2001[43]	Cumulative incidence rates of microvascular complications: 2y screening: Blindness: 3.06%; ESRD: 0.19%; LEA: 0.97% 5y screening: Blindness 3.13%; ESRD: 0.19%; LEA: 0.99% Control (no screening): Blindness: 4.3%; ESRD: 0.54%; LEA: 1.43% NSD between 2 and 5-y screening Cost-effectiveness (cost/QALY): 2-y: $17,833; 5-y: $10,531 Incremental cost/QALY: lowest 40-49y group ($9,193), highest 70y+ ($36,467)	Mass screening is CE compared to opportunistic screening Costs incurred with mass screenings are offset with life-years gained Mass screening for DM2 is relatively CE compared to other screening interventions (e.g. cervical cancer or HTN) Screening is more CE in younger than older patients	Lack of transparency for assumptions, data synthesis No sensitivity analyses Do not include CVD risk reduction in model Do not include adverse effects of screening

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	Objective	Type of screening; Perspective	Type of model	Population; Country	Included costs	Discount rate
Hoerger et al, 2004[87]	To estimate the incremental cost-effectiveness of two diabetes screening strategies: targeted to people with HTN and universal screening	One-time opportunistic screening during regular physician visit Targeted to persons with HTN Single payer health care system Not an economic study	Markov model with cohort simulation; is an update of the CDC model (CDC Diabetes Group 2002); considers 5 complications: nephropathy, neuropathy, retinopathy, coronary heart disease, stroke	General primary care population based on census United States	Direct medical costs: screening, diagnostic tests, treatment	3% annual rate
Glumer et al, 2006[93]	To describe the uncertainties in estimates of the cost-effectiveness of screening for DM2 where the outcome is CHD risk	NR; appears to be health care system perspective	Population-based simulation model	Based on community sample age 30-60y Denmark	Screening and treatment for DM2 and complications	0
Waugh et al, 2007[13] Health Technology Assessment	To quantify the trade-off between the costs and benefits of screening and early treatment	Population screening National Health Service	Markov model	United Kingdom general population 40-70 y	Screening and treatment for DM2 and complications	3.5% for costs and benefits

Abbreviations: BG, blood glucose; BP, blood pressure; CDC, Center for Disease Control; CE, cost effectiveness; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DCCT, Diabetes Control and Complications Trial; DM1, type 1 diabetes; DM2, type 2 diabetes; ESRD, end-stage renal disease; FPG, fasting plasma glucose; HOT, Hypertension Optimal Trial; HTN, hypertension; LEA, lower extremity amputation; NA, Not applicable; NHANES, National Health and Nutrition Examination Survey; NR, not reported; NSD, no significant difference; OGTT, oral glucose tolerance test; QALY, quality-adjusted life year; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; UKPDS, United Kingdom Prospective Diabetes Study; US, United States; y, year.

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	Base case assumptions	Time horizon	Data sources	Sensitivity analyses	Intervention
Hoerger et al, 2004[87]	In the absence of screening, DM2 diagnosed on average 10y after onset; one-time screening makes diagnosis 5y after onset; with targeted screening only people with HTN are screened; with universal screening all persons are screened; 47% of people age 45-74 have HTN; intensive BP control adds as much benefit to DM2 as to prediabetes; RRR CHD events 51%; initially screening by capillary blood glucose with (+) followed by FPG which is repeated if (+); assume 100% sensitivity and specificity of FPG; intensive glycemic control after diagnosis	Lifetime; Cost/QALY	UKPDS, HOT trial, US Census data	One-way sensitivity analysis for age 55y, examining 129 critical parameters: findings were robust to treatment costs, screening costs, screening lead time, effect of HTN therapy	Treatment of HTN to goal of DBP 80mm Hg (HOT); intensive glycemic control for diagnosed DM2 (UKPDS)
Glumer et al, 2006[93]	Overall compliance rates from 30 to 75%; risk prediction for CHD events from the UKPDS; risk reductions in screened populations same as those in RCTs of various diabetes-related treatments; examine 2 extreme scenarios for assumption on how single CVD risk factor reductions combine when more than 1 factor is treated:combined therapy only as effective as most effective single agent and where risk reductions combine in a multiplicative manner	5y	UKPDS, Danish Inter99 study (population data), other RCTs	Model not sensitive to decisions about which groups to screen nor to costs of screening or treatment; model strongly affected by assumptions about how treatments combine to reduce risk	Optimal treatment of screen-detected persons; details not provided
Waugh et al, 2007[13] Health Technology Assessment	Onset of DM2 A1c is 5.9%; preclinical phase 11y; prevalence of undiagnosed DM2 1.4 to 4.4%; 14% CHD risk reduction per 1% fall in A1c (per UKPDS); prevalence of diagnosed CVD negligible (would have been screened)	40y	UKPDS CVD risk engine; other sources	Rate of A1c progression, risk reduction with glycemic control; various treatment regimes; costs	Screening with A1c followed by OGTT if A1c > 5.7% Various interventions for hyperglycemia, HTN, lipids

APPENDIX B5. STUDIES MODELING SCREENING FOR TYPE 2 DIABETES (KQ1)

Author, Year (in date order)	**Outcomes**	**Conclusions**	**Quality assessment**
Hoerger et al, 2004[87]	Results per true diabetes case, compared to no screening, with intensive glycemic control and intensified HTN control after diagnosis: Targeted screening for people with HTN only: QALYs gained per person screened (cost/QALY) ranged from 0.08 with screening at 35y ($87,096), to 0.23 for screening at 65y ($31,228) Universal screening: QALYs gained per person screened (cost/QALY) ranged from 0.05 with screening at 35y ($126,238), to 0.11 for screening at 75y ($48,146) Universal vs. targeted screening, incremental cost/QALY: 35y: $143,830; 75y $443,433 Universal vs targeted screening: Relative to targeted screening, universal screening has high cost-effectiveness ratios which increase with age	Targeted screening to persons with HTN is more CE than universal screening at every age when each alternative is compared to no screening Targeted and universal screening are more CE when take into account reduction in CHD events from earlier treatment of HTN for ages 55, 65, 75 than for 35 and 45y The most CE approach to one-time screening: target people with HTN 55 to 75y Benefit of screening comes mainly from reducing CHD events by control of HTN rather than from reducing microvascular complications	Did not include adverse effects of screening Thorough sensitivity analyses Includes submodels for CVD and stroke Includes benefits for tight BP control, but not other CVD risk reduction interventions Assumes 100% uptake and follow-up
Glumer et al, 2006[93]	Least conservative model (low costs and multiplicative risk reduction for combined treatments): CE ratio: 23,000 to 82,000 pounds; major contributors to uncertainty: risk reduction for hypertension treatment and UKPDS risk model intercept	There is considerable uncertainty about the cost-effectiveness of screening for DM2; the most important parameter is the effect of treatment and whether risk reductions are multiplicative or additive	Model combines effects of treatment of hyperglycemia, hypertension and dyslipidemia Time horizon 5y
Waugh et al, 2007[13] Health Technology Assessment	Cost reduction and QALYs gained from fewer CVD events, largely from statin treatment, as well as fewer microvascular complications Incremental cost per QALY £2,266 for base case (40-70y) CE greatest for 60-69y: cost per QALY £1,152	Screening is relatively cost effective for persons 40-70y of age; more cost-effective for the older group and for persons with hypertension or obesity	Includes macro and microvascular complications; relatively simple model

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)* Whelton et al, 2005[103] ALLHAT Officers, 2002[115] Barzilay et al, 2001[231]	BP treatment (pharmacology)	United States, Canada, Puerto Rico, Virgin Islands Primary care clinics, hypertension clinics (623 centers) February 1994 - March 2002	Overall study: Total n = 42,418 Chlorthalidone = 15,255 Amlodipine = 9048 Lisinopril = 9054 Doxazosin = 9061 (this arm discontinued early because RR of heart failure high) Treatment assignment for DM subgroup (only from Barzilay 2001) DM total n = 15,297 (36%) DM on chlorthalidone = 5535 DM on amlodipine = 3327 DM on lisinopril = 3217 DM subgroup analysis (excluding doxazosin arm): Total n = 31,512 DM = 13,101 IFG = 1399 NG = 17,012	4.9 y (mean)	Age ≥ 55 --Stage 1 or 2 HTN --1 additional CHD risk factor or past history of atherosclerotic CVD	History of CHF and/or LVEF < 35% Symptomatic MI, angina, or CV event within last 6 months Serum Cr ≥ 2 HTN resistant to > two drugs BP > 180/110 on two separate readings Requirement for study drugs for non-HTN indications

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)* Whelton et al, 2005[103] ALLHAT Officers, 2002[115] Barzilay et al, 2001[231]	Unknown	Provider selected, most identified by chart review	**DM subgroup info:** %Black: --DM 39% --IFG 30% --NG 32% Age: --DM 67(7) --IFG 67(8) --NG 67(8) % male: --DM 51% --IFG 62% --NG 55% **Overall group:** Race --White 47% --Black 32% --White Hispanic 13% --Black Hispanic 3% --Other 5% Age: mean (SD) (y) --66.9(7.7) % male --53%	DM subgroup analysis: Fasting BS ≥ 126, with DM agents in last 2y, nonfasting baseline BS ≥ 200 IFG 110-125 and no history of DM NG - no history of DM and baseline BS < 110	Unknown	DM subgroup analysis: Atherosclerotic CVD --DM 36% --IFG 63% --NG 62% LVH --DM 15% --IFG 26% --NG 27% Baseline history of CHD --DM 20% --IFG 31% --NG 17%	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)* Whelton et al, 2005[103] ALLHAT Officers, 2002[115] Barzilay et al, 2001[231]	DM subgroup from Barzilay 2001: TC --203-227 LDL --128-150 (unavailable for overall group) HDL --39-53 (unavailable for overall group) DM subgroup analysis: History of HDL < 35 --DM 9% --IFG 18% --NG 13%	SBP/DBP --DM 147/83 (15/10) --IFG 147/85 (16/10) --NG 146/85 (16/10) % on antiHTN meds --DM 92% --IFG 89% --NG 89% Baseline values by intervention category is not available for diabetes subgroup	Smoking: --DM 13% --IFG 24% --NG 28% BMI mean (SD): --DM 31 (6) --IFG 31 (6) --NG 29 (6) % taking aspirin: --DM 34% --IFG 38% --NG 38%	Trial is in two parts: HTN trial is comparative effectiveness: Step 1 - study drug --chlorthalidone vs lisinopril, amlodipine, (or doxazosin) --the doxazosin arm stopped prematurely Step 2 - addition of open-label atenolol, clonidine, or reserpine Step 3 - addition of hydralazine (or other study drugs)	Primary: fatal CHD or nonfatal myocardial infarction Secondary: all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization, or hospitalized angina), and combined cardiovascular disease (combined CHD, stroke, other treated angina, heart failure, peripheral arterial disease), end-stage renal disease, and any of the above individually

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)* Whelton et al, 2005[103] ALLHAT Officers, 2002[115] Barzilay et al, 2001[231]	Comparisons listed as RR (p-value) Only significant comparisons listed - all others are nonsignificant. Amlodipine/chlorthalidone: --higher risk of heart failure in DM group 1.39 (<.001) and NG group 1.30 (.001), and marginally increased risk in IFG group 1.66 (.06) --higher risk of CHD in IFG group 1.73 (.02)	Lisinopril/chlorthalidone: --marginally higher risk of heart failure in DM group 1.15 (.06) and significantly higher risk in the NG group 1.19 (.03) --higher risk of stroke in NG group 1.31 (.003) --higher risk of combined CVD in NG group 1.13 (.001)	After 5y, adherence to lisinopril compared with chlorthalidone was worse in all 3 glycemic strata % dropping assigned study medication (lisinopril vs chlorthalidone): --DM 17% vs 14% --IFG 16% vs 9% --NG 16% vs 12% Details about reasons for withdrawal NR	Overall group data (NR for DM subgroup): Angioedema - chlorthalidone (0.1%) Amlodipine (<.01%) Lisinopril (0.4%) One death from angioedema in the lisinopril group No differences in gastrointestinal bleed rates amongst groups

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
ALLHAT-LLA (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Arm)* ALLHAT Officers, 2002[115]	Lipid treatment (pharmacology)	See above 513 eligible clinics	Total n = 10,355 Pravastatin = 5170 Usual care = 5185 The only DM specific information available is from Barzilay 2001 paper. Total n (including doxazosin group) = 3635 Pravastatin = 1854 Usual care = 1871	4.8 y (mean)	Enrollment in HTN trial LDL 120-189 mg/dL (or 100-129 mg/dL if known CHD), and TG ≤ 350 mg/dL	Current lipid-lowering treatment Secondary causes of hyperlipidemia ALT > 2 ULN Enrollment "discouraged" for those whose physicians recommended cholesterol lowering treatment
ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial)* Sever et al, 2003,[116] 2005[118]	Lipid treatment (pharmacology)	United Kingdom, Ireland, Denmark, Iceland, Sweden Primary care centers 1998 - 2000	Total population: Atorvastatin: 5168 Placebo: 5137	3.3y (median)	Age 40-79 with either untreated (>160/100 mm/Hg) or treated (>140/90 mg/Hg) HTN; TC ≤ 251 mg/dL (≤ 6.5 mmol/l); no statin or fibrate use. Patients had to have at least 3 of the following: left ventricular hypertrophy, other EKG abnormality, DM2, peripheral arterial disease, previous stroke or transient ischemic attack, male, age ≥55, microalbuminuria or proteinuria, smoking, plasma total cholesterol/HDL ≥ 232 mg/dl (≥ 6 mmol/l), premature family history of CHD	Previous MI, treatment for angina at time of study, cerebrovascular event within 3m of study, fasting triglycerides > 395 mg/dL (4.5mmol/L), heart failure, uncontrolled arrhythmias, any clinically important hematological or biochemical abnormality

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
ALLHAT-LLA (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Arm)* ALLHAT Officers, 2002[115]	Unknown	Provider selected, most identified by chart review	No DM subgroup info available	DM subgroup analysis: Fasting BS ≥ 126, treatment with DM agents in last 2y, nonfasting baseline BS ≥ 200 IFG 110-125 and no history of DM NG - no history of DM and baseline BS < 110	Unknown	See above - no DM specific information in lipid substudy	NR
ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial)* Sever et al, 2003,[116] 2005[118]	NR	Recruitment method NR Of total n, about 53% were recruited from primary care practices and 47% from referral centers	Total population- Race: 94.6% white Mean age: I: 63.1y (SD 8.5) C: 63.2y (SD 8.6) Male: 81%	NA	NA	Previous stroke or TIA: I: 485/5168 (9.4%), C: 516/5137 (10.0%) Peripheral vascular disease: I: 261/5168 (5.1%), C: 253/5137 (4.9%) Other relevant CVD (not described): I; 188/5168 (3.6%), C: 207/5137 (4.0%) Mean (SD) number of cardiovascular risk factors: I: 3.7 (0.9), C: 3.7 (0.9)	Glucose: I: 112 mg/dL, SD 38 (6.2 mmol/L, SD 2.1) C: 112 mg/dL, SD 6.2 mmol/L, (SD 2.1)

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
ALLHAT-LLA (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Arm)* ALLHAT Officers, 2002[115]	DM specific information NA Baseline TC: I: 223.7 mg/dL (26.9), C: 223.7 mg/dL (26.7) LDL: I: 145.6 mg/dL (21.4), C: 145.5 mg/dL (21.3) HDL: I: 47.6 (13.4), C: 47.4 (13.6) TG: I: 150.6 (70.4), C: 152.8 (73.0) After 4 years follow-up: TC decreased 17.2% in I group, 7.6% in C group LDL decreased 27.7% in I group, 11.0% in C group HDL increased 3.3% in I group,	DM specific information NA Baseline BP SBP: I: 145 mmHg (13.8), C: 145 (14.0) DBP: I: 84 (9.8), C: 84 (9.8)	DM specific information not available Smoking: I: 23.1%, C: 23.3% Obesity: I: 42.8%, C: 42.5% History of CHD: I: 13.4%, C: 15.0%	I: pravastatin titrated to achieve 25% reduction in LDL cholesterol + diet C: diet, primary care physicians could prescribe LDL lowering treatment, but "vigorous therapy was discouraged" By year 6, 26% of control group participants were receiving a statin drug	Primary: all-cause mortality Secondary: fatal CHD or nonfatal myocardial infarction, cause-specific mortality, total and site-specific cancers, EKG evidence of myocardial infarction, health-related quality of life, major costs of medical care
ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial)* Sever et al, 2003,[116] 2005[118]	TC: 212 mg/dL (SD 31) both groups (5.5 mmol/L, SD 0.8) LDL: 131 mg/dL (SD 27) both groups (3.4 mmol/L, SD 0.7) HDL: 50 mg/dL (SD 15) both groups (1.3 mmol/L, SD 0.4) TG: I 149 mg/dL (SD 79) (1.7 mmol/L, SD 0.9), C 140 mg/dL (SD 79) (1.6 mmol/L, SD 0.9) On lipid-lowering treatment: I: 0.8%, C: 1.0% By the end of follow-up, LDL cholesterol was 29% lower in the intervention group compared to placebo	I: 164.2/95.0 (SD 17.7/10.3), C: 164.2/95.0 (SD 18.0/10.3) Any antiHTN use I: 4147/5168 (80.2%), C: 4141/5137 (80.6%)	Smoker: I: 1718/5168 (33.2%) C: 1656/5137 (32.2%) Left ventricular hypertrophy: I:744/5168 (14.4%), C:729/5137 (14.2%) EKG abnormalities other than left ventricular hypertrophy: I:741/5168 (14.3%), C:729/5137 (14.2%)	I: atorvastatin 10mg qd C: placebo qd The lipid trial was a substudy of a larger antihypertensive trial comparing a calcium channel blocker based regimen to a beta-blocker based regimen	To assess and compare the long-term effects on the combined endpoint of non-fatal MI (including silent MI) and fatal CHD Secondary endpoints: symptomatic MI + fatal CHD, all cause mortality, cardiovascular mortality, fatal and non-fatal stroke, heart failure, total coronary endpoints, total cardiovascular events and procedures

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
ALLHAT-LLA (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Arm)* ALLHAT Officers, 2002[115]	All cause mortality (pravastatin vs usual care - relative risk and confidence interval): --DM 1.03 (0.86-1.22) --nonDM 0.96 (0.84-1.11) CHD death + nonfatal myocardial infarction: --DM 0.89 (0.71-1.10) --nonDM 0.92 (0.76-1.10)	NR	After 6y, 23% were not receiving the study drug in the pravastatin group	Specific AE data not collected
ASCOT (*Anglo-Scandinavian Cardiac Outcomes Trial)* Sever et al, 2003,[116] 2005[118]	*All comparisons I vs C (including p-values)* Nonfatal MI + fatal CHD (including silent MI) - Primary endpoint 100/5168 (1.9%) vs 154/5137(3.0%) Rate/1000 patient y: 6.0 vs 9.4 HR 0.64 (0.50-0.83), p=0.0005 Total CV events and procedures 389/5168 (7.5%) vs 486/5137 (9.5%) Rate/1000 patient y: 24.1 vs 30.6 HR 0.79 (0.69-0.90), p=0.0005 Total coronary events 178/5168 (3.4%) vs 247/5137 (9.5%) Rate/1000 patient y: 10.8 vs 15.2 HR 0.71 (0.59-0.86), p=0.0005 Nonfatal MI (excluding silent MI) + fatal CHD 86/5168 (1.7%) vs 137/5137 (2.7%) Rate/1000 patient y: 5.2 vs 8.3 HR 0.62 (0.47-0.81), p=0.0005	CV mortality 74/5168 (1.4%) vs 82/5137 (1.6%) Rate/1000 patient y: 4.4 vs 4.9 HR 0.90 (0.66-1.23), p=0.5066 Fatal and non-fatal stroke: 89/5168 (1.7%) vs 121/5137 (2.4%) Rate/1000 patient y: 5.4 vs 7.4 HR 0.73 (0.56-0.96), p=0.0236 Fatal and non-fatal heart failure: 41/5168 (0.8%) vs 36/5137 (0.7%) Rate /1000 patient y: 2.5 vs 2.2 HR 1.13 (0.73-1.78), p=0.5794	Total withdrawals: I: 5, C: 9 Withdrawals due to AEs NR	No difference reported between groups One person in the I group developed rhabdomyolysis, but in the setting of high alcohol intake and a febrile illness

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
	See above	See above	DM population: Atorvastatin 1258 Placebo 1274	See above	See above	See above
CONVINCE (*Controlled ONset Varapamil Investigation of Cardiovascular Endpoints Trial)* Black et al, 2003[104]	BP treatment (pharmacology)	15 countries (North America, South America, Europe) "Clinical sites" 1996 - 1998	Total population: I :COER verapamil: 8241 C: Atenelol or hydrochlorothiazide: 8361	2-4.25 y (median 3 y)	Age >55 years; treatment for HTN or diagnosis of HTN: (current use of antihypertensive medication(s) for at least the past 2 months and BP 175/100 or no current use of antihypertensive medications or use of antihypertensive medications for < 2 m and 140 < SBP < 190 mm Hg or 90 < DBP < 110 mm Hg at the qualifying visit; presence of at least one of the following prior to randomization: history of MI (12m); history of stroke (6m) prior to randomization; history of cigarette use (current or within 3y); DM2; LVH by echocardiogram or electrocardiogram; low HDL (,35 mg/dL [,0.9 mmol/L]), high LDL (.159 mg/dL [.4.11 mmol/L]), or high TC (.250 mg/dL [.6.46 mmol/L]) on two occasions in the 5y prior to randomization; history of TIA with hospitalization; body weight >25% above ideal; presence of any known atherosclerotic vascular disease; presence of a vascular bruit	History of CHF, NYHA classification II - IV; cardiac dysrhythmias requiring medical treatment; secondary HTN due to any cause; sick sinus syndrome, heart block greater than first degree, bradycardia, or presence of Wolff-Parkinson-White or Lown-Ganong-Levine syndrome; other contraindications to either COER-verapamil or both HCTZ and atenolol; contraindication to either HCTZ or atenolol indicates eligibility; working an evening, night or alternating shift; known MI within 12 months or stroke within 6 months of randomization date; known renal impairment (serum creatinine > 2.0 mg/dL [> 177 mmol/L] or creatinine clearance , 30 mL/min); factors suggesting noncompliance with the protocol; a disease likely to cause death within 5y such as untreated malignancy; the investigator's clinical judgment that the patient will not achieve adequate BP control using a three-drug regimen; current SBP.190 mmHg or DBP.110mmHg without treatment by antihypertensive medication; medical condition at screening requiring treatment with any of the specific study medications; previous admission to the study; participation in another clinical trial of antihypertensive medications within 30 days of randomization

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
	NR	See above	DM population: White race: I: 1131/1258 (89.9%) C: 1163/1274 (91.3%) Mean age: I:63.6y (SD 8.5) C: 64.0y (SD 8.2) Male: I: 77.0% C: 75.6%	Patient self-report with DM treatment (including diet, oral hypoglycemics, insulin) OR baseline FBG >108 mg/dL (>6.0mmol/L) and 2-h value ≥200 mg/dL (≥11.1 mmol/L) after 75-g glucose load	Oral hypoglycemics: I:645/1258 (51.3%), C:683/1274 (53.6%) Insulin: I:92/1258 (7.3%), C:96/1274 (7.5%)	Previous stroke or TIA: I: 93/1258 (7.4%), C: 98/1274 (7.7%) Peripheral vascular disease: I: 70/1258 (5.6%), C: 65/1274 (5.1%) Other significant CVD: I: 50/1258 (4.0%), C: 43/1274 (3.4%) Mean (SD) number of CV risk factors: I: 4.1 (1.0), C: 4.0 (1.0)	Glucose: I: 155 mg/dL, (8.6 mmol/L, SD 2.8) C: 157 mg/dL, (SD 8.7 mmol/L, SD 2.8)
CONVINCE (*Controlled ONset Varapamil Investigation of Cardiovascular Endpoints Trial)* Black et al, 2003[104]	NR	Chart review at clinical site by participating physician	Total n = 16,476 Race: White - I: 84.2%, C: 84.5% Black - I: 6.9%, C: 6.8% Asian - I: 1.2%, C: 1.2% Hispanic - I: 7.3%, C: 7.0% Other - I: 0.4%, C: 0.5% Mean age I: 65.5 (SD 7.4), C: 65.6 (SD 7.4 Male: I 43.8%, C: 44.2%	NR	NR	Total population- Previous MI: I: 607/8179 (7.5%), C: 652/8297 (7.9%) Established vascular disease: I: 1362/8179 (16.7%), C: 1387/8297 (16.8%) Stroke: I: 370/8179 (4.5%), C: 393/8297 (4.8%) TIA: I: 184/8179 (2.3%), C: 162/8297 (2.0%)	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
	TC: 205 mg/dL, SD 31 both groups (5.3 mmol/L, SD 0.8) LDL: I 127 mg/dL, SD 27 (3.3 mmol/L, SD 0.7), C 127 mg/dL, SD 31 (3.3 mmol/L, SD 0.8) HDL: 46 mg/dL, SD 12 both groups (1.2 mmol/L, SD 0.3) TG: 166 mg/dL, SD 87 both groups (1.9 mmol/L, SD 1.0) On lipid-lowering treatment: I: 1.1%, C: 1.6% By the end of follow-up, LDL cholesterol was 29% lower in the intervention group compared to placebo	I: 165.1/92.9 (SD 17.6/10.3), C: 164.8/92.4 (SD 17.1/10.3) Any antiHTN use I: 1069/1258 (85%), C: 1065/1274 (83.6%	Smoker: I: 257/1258 (20.4%) C: 258/1274 (20.3%)	I: atorvastatin 10mg qd C: placebo qd By end of the study, 14% in placebo group were receiving open-label statins and 84% of those originally assigned a statin were still taking one	See above
CONVINCE (*Controlled ONset Varapamil Investigation of Cardiovascular Endpoints Trial)* Black et al, 2003[104]	NR	I: 150.1/86.8 (SD 15.8/9.8), C: 150.1/86.8 (SD 16./9.8)	Obesity: I: 4150/8179 (51.0%), C: 4096/8297 (49.6%) Dyslipidemia: I: 2540/8179 (31.2%), C: 2575/8279 (31.2%) Vascular bruit: I: 403/8179, C: 409/8297 (5.0%)	COER verapamil 150mg qd (evening) vs atenolol or hydrochlorthiazide Hydrochlorthiazide, if necessary, could be added to regimen of patients receiving COER verapamil or atenolol, and atenolol could be added to those receiving initial hydrochlorthiazide	To compare the 2 regimens in preventing acute MI, stroke or CVD death Secondary: expanded CVD endpoint to include: hospitalization for angina, cardiac revascularization or transplant, heart failure, transient ischemic attack or carotid endarterectomy, accelerated or malignant hypertension, renal failure; all-cause mortality; cancer; hospitalization for bleeding (excluding hemorrhagic stroke); incidence of primary endpoint occurring between 6am-noon

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
	DM population: I vs C Nonfatal MI + fatal CHD (including silent MI) - Primary endpoint 38/1258 (3.0%) vs 46/1274 (3.6%) Rate/1000 patient y: 9.6 vs 11.4 HR 0.84 (0.55-1.29) Total CV events and procedures 118/1258 (9.2%) vs 151/1274 (11.9%) Rate/1000 patient y: 30.2 vs 39.1% HR 0.77 (0.61-0.98), p = 0.036	Fatal and non-fatal stroke 27/1258 (2.1%) vs 41/1274 (3.2%) Rate/1000 patient y: 68. vs 10.2 HR 0.67 (0.41-1.09) There were NSD in risk reduction when comparing diabetes and no diabetes groups for any of the above outcomes (p-value for heterogeneity all > 0.1) For the primary endpoint, the p-value for heterogeneity between diabetic patients and nondiabetic patients was 0.14)	30 patients had incomplete data; 4 vital data only at end of follow-up (reasoning NR)	No "excessive risk of adverse reactions" No significant differences in liver enzyme abnormalities No rhabdomyolysis
CONVINCE (*Controlled ONset Varapamil Investigation of Cardiovascular Endpoints Trial)* Black et al, 2003[104]	Total population Primary composite outcome: I vs C 364/8179 vs 365/8297 HR 1.02 (0.88-1.18; p=0.77) -Fatal or nonfatal MI: I vs C 133/8179 vs 166/8297 HR 0.82 (0.65-1.03; p=0.09) -Fatal or nonfatal stroke: I vs C 133/8179 vs 118/8297 HR 1.15 (0.90-1.48; p=0.26) -CV-related death: I vs C 152/8179 vs 143/8297 HR 1.09 (0.87-1.37; p=0.47)	DM vs non-DM - DM - RR 0.86 (0.66 - 1.12) non-DM - RR 1.10 (0.92 - 1.31) Interaction of diabetes treatment p = 0.16	Treatment withdrawals: I: 39.4%, C: 39.7% Participants in intervention group withdrew more often due to adverse events (p = 0.02) Withdrawals due to constipation: I: 216/8179, C: 28/8361	New cancer: I: 3.8%, C: 3.6 % HR 1.06 (0.91-1.24), p = .46 Death or hospitalization due to bleeding (not including intracerebral bleeding): I: 1.4%, C: 1.0% HR 1.54 (1.15-2.04), p = .003 Deaths from bleeding 0.1% in both groups Death or hospitalization due to serious AE: I: 16.9%, C: 16.4% HR 1.04 (0.97 - 1.12), p = 0.29

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
HPS (*Heart Protections Study)* HPS Collaborative Group, 2003[95]	Lipid treatment (pharmacology)	United Kingdom Study clinic (referral from general practitioner) 1994 - 1997	Simvastatin: 10269 Placebo: 10267	4.8y (mean)	Age 40-80 with nonfasting TC at least 135 mg/dl w/history of DM, coronary disease, occlusive disorder of noncoronary arteries or treated HTN (if also male and at least 65y)	Patients that general practitioner considered statin use to be clearly indicated or contraindicated, previous MI, stroke, hospital admission for angina within previous 6m; chronic liver disease or evidence of abnormal liver function, severe renal disease or evidence of substantially impaired renal function, inflammatory muscle disease or evidence of muscle problems, concurrent treatment with cyclosporin, fibrates or high-dose niacin, child-bearing potential, severe heart failure, life-threatening condition other than vascular disease or diabetes, conditions that might limit long-term compliance

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
HPS (*Heart Protections Study)* HPS Collaborative Group, 2003[95]	9.3y (mean) N=5348	Use of medical records to identify potentially eligible patients with cooperation of general practitioners	DM population (5963) vs non-DM population (14,573) (Note: DM population includes DM1 and DM2) Race: NR Age: 62.1 y (SD 8.9) vs 64.7 (SD 8.1) Male: 30% vs 22%	NR	DM2 population: Insulin: 25% Sulphonylureas: 42% Metformin: 31% None of these agents: 21%	DM population vs non-DM population: Prior M: 1125/5963 (19%) vs 7385/14573 (51%) Other CHD: 856/5963 (14%) vs 4020/14573 (28%) Other vascular: 1070/5963 (18%) vs 2930/14573 (20%)	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
HPS (*Heart Protections Study)* HPS Collaborative Group, 2003[95]	DM population vs non-DM population: TC: 220 mg/dL, SD 39.8 (5.7 mmol/L, SD 1.03) vs 228 mg/dL, SD 38.6 (5.9 mmol/L, SD 1.00) LDL: 124 mg/dL, SD 31.7 (3.2 mmol/L, SD 0.82) vs 131 mg/dL, SD 31.7 (3.4 mmol/L, SD 0.82) HDL: 41 mg/dL, SD 13.9 (1.06 mmol/L, SD 0.36) vs 41 mg/dL, SD 12.0 (1.06 mmol/L,SD 0.31) TG: 204 mg/dL, SD 61.4 (2.3 mmol/L, SD 1.59) vs 177 mg/dL, SD 49.0 (2.0 mmol/L, SD 1.27)	DM population vs non-DM population: 148/82 (SD 23/12) vs 143/81 (SD 24/12)	Smoker (ever): DM population vs non-DM population 4008/5963 (67%) vs 11354/14573 (78%)	I: simvastatin 40mg qd C: placebo	Vascular mortality and morbidity of a substantial LDL cholesterol reduction maintained for several years

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
HPS (*Heart Protections Study)* HPS Collaborative Group, 2003[95]	Non-DM population Major coronary events: I: 8.5% vs C: 11.5% Stroke: 4.0% vs 5.4% Revascularization: 9.3% vs 12.3% Major vascular events: 19.6% vs 25.2% DM population (Type 1 and 2 combined) Major coronary events: I: 9.4% vs C: 12.6% Stroke: I: 5.0% vs C: 6.5% Revascularization: I: 8.7% vs C: 10.4% Major vascular event: I: 20.2% vs C: 25.1% Risk reduction, I vs C (95% CI, p): Major coronary events --nonDM, 27% (19-34, <.0001) --DM, 27% (15-38, <.0001) -- reflected a 20% (4-34, .02) Reduction in coronary mortality Stroke --nonDM, 26% (14-36, .0002) --DM, 24% (6-39, .01) Revascularization --nonDM, 26% (18-33, <.0001) --DM, 17% (3-30, .02) Major vascular events --nonDM, 25% (19-30, <.0001) --DM, 22% (13-30, <.0001) No significant differences between DM and nonDM groups for outcomes above (p-value for heterogeneity all > 0.3)	Other subgroup comparisons on first major vascular event: --A comparison amongst subgroups of diabetic persons revealed no significant differences in risk reduction according to: sex, age, history of treated hypertension, BMI, duration of diabetes, or baseline level of glycemic control --Diabetic persons without CHD benefited to similar degree as those with CHD and no diabetes Risk reduction of first major vascular event associated with simvastatin use according to baseline features: --DM alone, RRR 32.9%, ARR 4.4%, p = .0003 --Occlusive arterial disease alone, RRR 24.5%, ARR 6.2%, p <.0001 --DM + occlusive arterial disease, RRR 18.4%, ARR 6.6%, p = .002	Compliance based on at least 80% of scheduled intervention taken at each follow-up (every 4 months for 1st y, then every 6 months) 82% simvastatin compliance, placebo NR Withdrawals: "about 1/6 stopped taking simvastatin"	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
Olivarius et al, 2001[98]	Disease manage-ment	Multi-center: 311 Danish practices (474 general practitioners)	Start of study: Routine care: 614 Structured care: 649 Analyzed for outcomes: Routine care: 415 Structured care: 459	6y (through January 1998)	Ages ≥ 40 y Newly diagnosed diabetes, defined as ≥126 mg/dL (≥ 7.0 mmol/l), between March 1989 - February 1991 Registered with a participating general practitioner	Life threatening somatic disease Mental illness Declined to consent Diagnosis not confirmed Non-white ethnicity

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
Olivarius et al, 2001[98]	Newly-diagnosed	Invitations sent to random sample of general practitioners; patients identified by screening through these general practitioners	Structured care vs routine care, respectively: % male: 52.4, 53.1 Median age: 65.5 (55.3-74.0), 65.3 (56.3-73.5) 100% White	Diagnosed by primary care physician and confirmed by FPG ≥ 126 mg/dL	Diabetes treatment methods varied per specific doctor's decisions, based on structured care approach	Structured care vs routine care %, respectively: History of myocardial infarction: 6.6, 7.7 Angina pectoris: 11.7, 11.9 History of stroke: 3.5, 4.2 Intermittent claudication: 3.9, 3.3 Amputation: 0.3, 0.2	Structured care vs routine care %, respectively: 10.2, 10.2

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
Olivarius et al, 2001[98]	Structured care vs routine care median, respectively: TC: 6.2, 6.2 Fasting TG: 2.03, 1.98	Structured care vs routine care median, respectively: BP: 150/85, 148/85	Structured care vs routine care median, respectively: BMI: 29.4/28.8 Current smokers: 35.5, 34.5 Former smokers: 31.3, 37.6 Never smokers: 33.2, 27.9 Note: Baseline variables for occupation and smoking habits were significantly different between I and C groups, p=0.01 and p=0.039 respectively	Routine care (national guidelines) vs structured care (routine care + additional 3 month questionnaires completed by doctor; 3 month consultations between patient and doctor discussing status and treatment goals; doctors received annual descriptive reports on patients; annual half day educational seminar for doctor; educational pamphlets distributed to patient)	Primary: Overall mortality and incidences of diabetic retinopathy, urinary albumin concentration $\geq$ 15 mg/l, myocardial infarction, and stroke Secondary: New peripheral neuropathy, angina pectoris, intermittent claudication, and amputation Tertiary outcomes: Levels of risk factors included in patient's goals Note: Focus of study to evaluate attitudes and opinions of doctors, risk factors, and varying treatment regimes, but provides 6 y morbidity and mortality outcomes of screen-detected population

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
Olivarius et al, 2001[98]	Nonfatal outcomes and mortality were the same in both groups (p< 0.01 is significant): Overall mortality p=0.82 Diabetic retinopathy p=0.55 Urinary albumin > 15 mg/l p=0.04 MI p=0.40 Stroke p=0.95 Peripheral neuropathy p=0.41 Angina pectoris p=0.68 Intermittent claudication p=0.96 Amputation p=0.35	Metformin was used more frequently in intervention group for 32 patients (10%) vs 14 patients (5), p=0.013	Structured care vs routine care #s, respectively: Death during study: 155, 164 Withdrew consent: 17, 17 Lost to follow-up: 18, 18	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
PPP (*Primary Prevention Project)* Sacco et al, 2003[96]	Aspirin and Vitamin E treatment	Italy outpatient and diabetic clinics 1994 - 1998	Aspirin: 519 Vitamin E: 509	3.6y (mean)	Age ≥ 50 with at least one major cardiovascular risk factor (age ≥ 65, HTN, hyperlipidemia, diabetes, obesity, family history of premature CHD)	Severe pathology; treatment with antiplatelet drugs (history of vascular events or disease); chronic use of antinflammatory agents or anticoagulants; chronic use of aspirin or vitamin E; disease with predictable poor short-term prognosis; predictable psychological or logistical difficulties affecting compliance with trial requirements
	See above	See above	See above	3.7y (mean)	See above	See above

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
PPP (*Primary Prevention Project)* Sacco et al, 2003[96]	NR	Recruited from general practitioner and diabetes clinics; method NR	DM population: Race: NR Age: 64.2 y (SD 7.5) Male: 48.2%	Fasting venous plasma glucose ≥140 mg/dL (≥7.8mmol/L) on at least two occasions or treatment with antidiabetic drugs	**Aspirin group:** *I: n=519* Diet: 141 Sulphonyloureas: 133 Metformin: 18 Sulphonyloureas + metformin: 169 Insulin + OHA: 47 Other: 11 *C: n=512* Diet: 137 Sulphonyloureas: 135 Metformin: 17 Sulphonyloureas + metformin: 166 Insulin + OHA: 48 Other: 9 **Vitamin E group:** *I n=509* Diet: 133 Sulphonyloureas: 147 Metformin: 14 Sulphonyloureas + metformin: 162 Insulin + OHA: 44 Other: 9 *C n=522* Diet: 145 Sulphonyloureas: 121 Metformin: 21 Sulphonyloureas + metformin: 173 Insulin + OHA: 51	DM population n=1031 HTN: 643 (62.4%) Hypercholesterolemia: 308 (29.9%)	NR
	See above	See above	non-DM population: Race: NR Age: 64.4y (SD 7.7) Male: 41.5%	See above	See above	Non-DM population n=3753 HTN: 2580 (68.8%) Hypercholesterolemia: 1498 (39.9%) (both of these significantly more frequent than in DM group)	See above

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
PPP (*Primary Prevention Project)* Sacco et al, 2003[96]	DM population: TC: 224.6 (SD 44.0) HDL: 49.8 (SD 16.2) TG: 175.1 (SD 105.9)	DM population: 148.7/84.9 (SD 17.1/9.0) antiHTN treatment: 624/1031	DM population: BMI 29.0 (SD 5.0) Current smoker: 168/1031 3 or more CV risk factors: 613 (59.5%)	Aspirin 100mg qd Vitamin E 300 mg qd	Reduction in the incidence of major CV and cerebrovascular events (CV deaths, nonfatal MI, nonfatal stroke)
	Non-DM population: TC: 237.8 (SD 44.7) HDL: 53.8 (SD 17.0) TG: 149.7 (SD 80.4) (Total and HDL cholesterol significantly higher than in DM group, and TG's significantly lower than in DM group)	Non-DM population: 144.6/85.5 (SD 16.0/8.4) antiHTN treatment: 2523/3753	Non-DM population: BMI 27.3 (SD 4.5) Current smoker: 555/3753 3 or more CV risk factors: 849 (22.6%) Many fewer - about 60% less- in the nonDM group had multiple CV risk factors as compared to the DM group	See above	See above

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
PPP (*Primary Prevention Project)* Sacco et al, 2003[96]	DM population - aspirin vs no aspirin Main combined endpoint 3.9% vs 4.3% RR 0.90 (0.50-1.62) Total CV events 10.2% vs 11.5% RR 0.89 (0.62-1.26) CV deaths 1.9% vs 1.6% RR 1.23 (0.49-3.10) MI 1.0% vs 2.0% RR 0.49 (0.17-1.40) Stroke 1.7% vs 2.0% RR 0.89 (0.36-2.17) Angina: 3.1% vs 3.9% RR 0.80 (0.39-1.64) TIA: 1.7% vs 2.4% RR 0.69 (0.27-1.79) Peripheral artery disease 2.6% vs 3.2% RR 0.83 (0.38-1.84)	DM population - Vitamin E vs no Vitamin E Main combined endpoint 4.3% vs 3.8% RR 1.13 (0.62-2.04) Total CV events 10.0% vs 11.7% RR 0.86 (0.60-1.22) CV deaths 2.0% vs 1.5% RR 1.28 (0.51-3.22) MI 1.4% vs 1.5% RR 0.90 (0.33-2.46) Stroke 1.6% vs 2.1% RR 0.75 (0.30-1.83) Angina 3.4% vs 3.6% RR 0.93 (0.45-1.90) TIA 1.5% vs 2.7% RR 0.54 (0.21-1.43) Peripheral artery disease 2.4% vs 3.4% RR 0.71 (0.32-1.58)	NR	Nonfatal bleeding higher with aspirin use 1.9 vs 0.2%; p=0.007 for aspirin vs no aspirin
	Non-DM population - aspirin vs no aspirin Main combined endpoint 1.6% vs 2.7% RR 0.59 (0.37-0.94) Total CV events 5.3% vs 7.5% RR 0.69 (0.53-0.90) CV deaths 0.4% vs 1.3% RR 0.32 (0.14-0.72) MI 0.8% vs 1.2% RR 0.69 (0.36-1.35) Stroke 0.6% vs 0.1% RR 0.59 (0.28-1.25) Angina 2.7% vs 3.1% RR 0.85 (0.56-1.28) TIA 1.4% vs 2.0% RR 0.71 (0.41-1.22) Peripheral artery disease 0.4% vs 1.0% RR 0.38 (0.15-0.99)	Non-DM - Vitamin E vs no Vitamin E Main combined endpoint 2.2% vs 2.1% RR 1.03 (0.66-1.60) Total CV events 6.3% vs 6.5% RR 0.97 (0.74-1.26) CV deaths 0.7% vs 1.0% RR 0.73 (0.36-1.47) MI 1.0% vs 1.0% RR 0.95 (0.49-1.82) Stroke 1.0% vs 0.6% RR 1.51 (0.72-3.15) Angina 3.3% vs 2.6% RR 1.29 (0.85-1.95) TIA 1.8% vs 1.6% RR 1.09 (0.63-1.87) Peripheral artery disease 0.4% vs 1.0% RR 0.37 (0.14-0.96)	NR	See above

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Topic of study	Country/ Setting/ Year(s) of study	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria
PROSPER (*Prospective Study of Pravastatin in the Elderly at Risk trial)* Shepherd et al, 2002[117]	Lipid treatment (pharmacology)	Scotland, Ireland, Netherlands Setting not specified 1997 - 1999	Pravastatin: 2891 Placebo: 2913	3.2 y (mean)	Age 70-82 Pre-existing vascular disease or higher risk for vascular disease because of smoking, HTN, or diabetes TC: 155 - 348 mg/dL (4.0 - 9.0 mmol/L) Triglycerides < 531 mg/dL (6.0 mmol/L)	After run-in period, those using less than 75% or more than 120% of assigned treatment were excluded Poor cognitive function
WHI (*Women's Health Initiative)* Ridker et al, 2005[97]	Aspirin treatment	United States Community-based, primary-care feasible 1992 - 2004	Aspirin: 19,934 Placebo: 19,942	8.1y (mean)	Age ≥ 45, female	History of: CHD, cerebrovascular disease, cancer, other major chronic illness History of side effects to aspirin or vitamin E Regular NSAID, vitamin A, vitamin E, or beta-carotene use Anticoagulant or steroid use

Abbreviations: AE, adverse effect; ALT, alanine aminotransferase test; ARR, absolute risk reduction; BMI, body mass index; BP, blood pressure; BS, blood sugar; C, control group; CABG, Coronary artery bypass graft; CHD, coronary heart disease; CHF, congestive heart failure; COER, controlled-onset extended-release; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DM2, type 2 diabetes; EKG, electrocardiogram; FBG, fasting blood glucose; FPG, fasting plasma glucose; GI, gastrointestional; HCTZ, hydrochlorothiazide; HDL, high density lipoprotien cholesterol; HPS, Heart Protection Study; HR, hazard ratio; HTN, hypertension; I, intervention group; IFG, impaired fasting glucose; LDL, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; N, number of participants in study; NA, not applicable; NG, normoglycemic; NR, not reported; NSAID, Non-Steroidal Anti-Inflammatory Drug; NSD, no significant difference; NYHA, New York Heart Association; OHA, Oral Hypoglycaemic Agent; qd, daily; RR, relative risk; RRR, relative risk reduction; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; TIA, transient ischemic attack; ULN, upper limit of normal; y, year.

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Duration of DM2	Participant selection	Population	Diabetes diagnosis	Diabetes treatment	Existing vascular disease	FBG (mg/dl) A1c (%)
PROSPER (*Prospective Study of Pravastatin in the Elderly at Risk trial)* Shepherd et al, 2002[117]	NR	NR	Total n = 5804 Diabetic subgroup: 11% I: 320/2891, C: 303/2913 Race: NR % male: 48 Mean age (SD): I: 75.4 (3.3), C: 75.3 (3.4)	NR	NR	History of angina: I: 806/2891 (27.9%), C: 753/2913 (25.8) History of claudication: I: 198/2891 (6.8%), C: 192/2913 (6.6%) History of myocardial infarction: I: 377/2891 (13.0%), C: 399/2913 (13.7%) History of stroke or TIA: I: 328/2891 (11.3%), C: 321/2913 (11.0%) History of angioplasty or CABG: I: 129/2891 (4.5%), C: 108/2913 (3.7%) History of peripheral vascular disease surgery: I: 67/2891 (2.3%), C: 56/2913 (1.9%) History of vascular disease: I: 1306/2891 (45.2%), C: 1259/2913	NR
WHI (*Women's Health Initiative)* Ridker et al, 2005[97]	NR	Volunteers recruited through mass mailing to female health professionals	Female health professionals Diabetes subgroup: 2.6% I: 538/19,934, C: 499/19,942 Age: 54.6 (7.0) in both groups Race: NR % male: 0% ≥ 65: 10%	NR	NR	None - history of CHD or cerebrovascular disease were exclusion criteria History of peripheral vascular disease not reported, but likely minimal	NR

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Lipids (mg/dl)	Blood pressure (mm Hg)	Other CVD risk factors	Intervention	Primary endpoint(s)
PROSPER (*Prospective Study of Pravastatin in the Elderly at Risk trial)* Shepherd et al, 2002[117]	TC (both groups): 220 mg/dL, SD 34.7 [5.7 mmol/L, SD 0.9] LDL (both groups): 147 mg/dL, SD 30.9 [3.8 mmol/L, SD 0.8] HDL (both groups): 50 mg/dL, SD 11.6 [1.3 mmol/L, SD 0.3] TG (both groups): 133 mg/dL, SD 27.0 [1.5 mmol/L, SD 0.7] % on lipid meds: NR Baseline values for I and C separately	I: 154.7/83.6 (21.9/11.2), C: 154.6/83.9 (21.8/11.7)	Smoker: I: 753/2891 (26.0%), C: 805/2913 (27.6) History of HTN: I: 1799/2891 (62.2%), C: 1793/2913 (61.6%)	I: Pravastatin 40 mg/day C: placebo daily	Primary endpoint: combined outcome CHD mortality, non-fatal myocardial infarction, fatal or non-fatal stroke Secondary outcomes: each of the above components examined separately Tertiary outcomes: included TIA, disability, and cognitive function
WHI (*Women's Health Initiative)* Ridker et al, 2005[97]	Hyperlipidemia defined as TC ≥ 240 mg/dL or self-reported physician-diagnosed hyperlipidemia with hyperlipidemia: I: 5960/19,934 (29.9%) C: 5803/19,942 (29.1%)	<130/85 mm Hg: I: 12,838/19,934 (64.4%), C: 12,903/19,942 (64.7%) 130-139/85-89 mm Hg: I: 3887/19,934 (19.5%), C: 3849/19,942 (19.3%) ≥ 140/90: I: 3209/19,934 (16.1%), C: 3171/19,942 (15.9%)	Current smokers: I: 2591/19,934 (13.0%), C: 2652/19,942 (13.3%) Obese: I: 3648/19,934 (18.3%), C: 3629/19,942 (18.2%) Family history premature MI: I: 2591/19,934 (13.0%), C: 2573/19,942 (12.9%) 10y Framingham risk: < 5.0%: I: 16,824/19,934 (84.4%), C: 16,871/19,942 (84.6%) ≥ 10.0%: I: 777/19,934 (3.9%), C: 818/19,942 (4.1%)	I: Aspirin 100 mg every other day C: placebo	Primary endpoint: combination of CHD death, non-fatal MI, non-fatal stroke Secondary endpoints: included individual end points of fatal or nonfatal MI, fatal or nonfatal stroke, ischemic stroke, hemorrhagic stroke, CHD death Tertiary end points: included all-cause mortality, transient ischemic attack, need for coronary revascularization

APPENDIX B6: DIABETES VS. NONDIABETES EVIDENCE TABLE OF TRIALS (KQ2)

Study; Author, year	Outcomes	Outcomes, continued	Adherence withdrawals (%)	Adverse Events
PROSPER (*Prospective Study of Pravastatin in the Elderly at Risk trial)* Shepherd et al, 2002[117]	Primary outcome: I: 408/2891 (14.1%), C: 473/2913 (16.2%) HR: 0.85 (0.74-0.97), p = 0.014 95% CI Primary endpoint - DM group: I: 70/303 (23.1%), C: 59/320 (18.4%) NonDM group: I: 338/2588 (13.1%), C: 414/2593 (16.0%) HR: 1.27 (0.90 - 1.80), p-value for interaction 0.015 CHD mortality or non-fatal myocardial infarction (including silent and unrecognized events): I: 292/2891 (10.1%), C: 356/2913 (12.2%) HR: 0.81 (0.69 - 0.94), p = 0.006 Fatal or non-fatal stroke: I: 135/2891 (4.7%), C: 131/2913 (4.5%) HR: 1.03 (0.81 - 1.31), p = 0.81	CHD mortality or non-fatal myocardial infarction (excluding silent and unrecognized events): I: 193/2891 (6.7%), C: 246/2913 (8.4%) HR: 0.77 (0.64 - 0.93), p = 0.007 CHD mortality: I: 94/2891 (3.3%), C: 122/2913 (4.2%) HR 0.76 (0.58 - 0.99), p = 0.043 All-cause mortality: I: 298/2891 (10.3%), C: 306/2913 (10.5%) HR: 0.97 (0.83 - 1.14), p = 0.74 At 2y follow-up, pravastatin induced decrease in LDL cholesterol was 27%	Discontinued: I: 724/2891, C: 725/2913 Non-fatal adverse events: I: 107/2891, C: 116/2913	Rhabdomyolysis: none in either group Cancer: HR for new cancer diagnosis I vs C: 1.25 (1.04 - 1.51), p = 0.02 Myalgias: I: 36/2891, C: 32/2913
WHI (*Women's Health Initiative)* Ridker et al, 2005[97]	Total event rates: Major CV event: I: 477/19,934, C: 522/19,942 RR 0.91 (0.80 - 1.013), p = 0.13 Stroke: I: 221/19,934, C: 266/19,942 RR 0.83 (0.69 - 0.99), p = 0.04 DM vs non-DM: Major CV event - DM group: I: 58/538, C: 62/499 RR 0.9 (0.63 - 1.29), p = 0.57 Major CV event - nonDM group: I: 418/19,396, C: 460/19,433 RR 0.9 (0.79 - 1.03). p = 0.13 Stroke - DM group: I: 15/538, C: 31/499 RR 0.46 (0.25 - 0.85), p = 0.01 Stroke - nonDM group: I: 206/19,396, C: 235/19,433 RR 0.87 (0.72 - 1.05), p = 0.15	Other than age and smoking status, there was no evidence of interaction between any of the other risk factors considered, including diabetes, and treatment effects	NR	No DM specific numbers Gastrointestinal bleeding: I: 910/19,934 (4.6%), C: 751/19,942 (3.8%) RR 1.22 (1.10 - 1.34), p , 0.001 Peptic ulcer: 542/19,934 (2.7%), C: 413/19,942 (2.1%) RR 1.32 (1.16 - 1.50), p < 0.001 Hematuria: I: 3,039/19,934 (15.2%), C: 2,879/19,942 (14.4%) RR 1.06 (1.01 - 1.12), p = 0.02 Easy bruising, epistaxis, and any report of gastric upset were also significantly more common in the aspirin group There were 5 fatal GI bleeds, 2 in the aspirin group and 3 in the placebo group

APPENDIX B7. DIABETES VS. NONDIABETES EVIDENCE TABLE OF SYSTEMATIC REVIEWS (KQ2)

Author, year *Quality rating*	Aims	Included studies	Time period covered	Eligibility criteria	Length of follow-up	N
Blood Pressure Lowering Treatment Trialists' Collaboration, 2005[107] *Fair*	Meta-analysis to compare effects of different BP lowering regimens on cardiovascular events and death in patients with and without DM	AASK ABCD (H) ABCD (N) HOPE HOT INDT LIFE NICOLE PART2 PREVENT PROGRESS RENAAL SCAT SCOPE SYST-EUR UKPDS-HDS	NR - 2003	Must meet one of the below criteria: 1) Randomization of patients between a BP lowering agent and a control (placebo or less intensive BP lowering regimen) or 2) Randomization of patients between regimens based on different classes of BP lowering drugs Trials must also: ≥ 1000 patient-years of planned follow up in each randomized group Must not have presented or published main results before finalization of the overview protocol in July 1995 Must not have aspirin or cholesterol lowering regimens added to the BP lowering regimen	2.6 - 8.4y	Total: 158,709 DM: 33,395 NonDM: 125,314
Costa et al, 2006[119] *Good*	Meta-analysis to evaluate clinical benefits of lipid lowering drug treatment in patients with and without DM, for primary and secondary prevention	AFCAPS/TexC ALLHAT-LLA ASCOT-LLA HHS HPS PROSPER	1966 - April 2004 (MEDLINE); 1980 - April 2004 (Embase); through issue 2, 2004 (Cochrane Central)	Lipid lowering/cholesterol drug arm Placebo arm Adequate concealment of random allocation Double blind assessment, including clinical outcomes ≥ 500 patients per group Type 2 diabetic and non-diabetic patients in both arms Follow up of ≥ 3 y Cardiovascular event as primary or secondary endpoint Provision for allowing calculation of individual results for DM vs nonDM groups Those with and without previous coronary artery disease (to evaluate primary and secondary prevention)	≥ 3y	80,862

Abbreviations: AASK, African-American Study of Kidney Disease and Hypertension Trial; ABCD (H), Appropriate Blood Pressure Control in Diabetes trial (hypertensive subgroup); ABCD (N), Appropriate Blood Pressure Control in Diabetes trial (non-hypertensive subgroup); ACE-I, angiotensin-converting enzyme-inhibitor; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLA, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial--Lipid Lowering Arm; ARBs, angiotensin II receptor blockers; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm; BP, blood pressure; CHD, coronary heart disease; COER, controlled onset extended release; DM, diabetes; GITS, gastrointestinal transport system; HDL, high density lipoprotein; HOPE, Heart Outcomes Prevention Evaluation study; HOT, Hypertension Optimal Treatment study (continued)

APPENDIX B7. DIABETES VS. NONDIABETES EVIDENCE TABLE OF SYSTEMATIC REVIEWS (KQ2)

Author, year *Quality rating*	Characteristics of included articles: study design / interventions / treatment	Outcomes	Main results	Adverse events
Blood Pressure Lowering Treatment Trialists' Collaboration, 2005[107] *Fair*	RCT Angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, and diuretics/beta-blockers: ramipril, perindopril, indapamide, enalapril maleate, amlodipine, nisoldipine, nitrendipine, irbesartan, losartan potassium, atenolol, candesartan, metoprolol, lisinopril, chlorthalidone, hydrochlorothiazide, captopril, atenolol, COER verapamil, lacidipine, nifedipine GITS, amiloride, nicardipine, trichlormethiazide, diltiazem, felodipine, isradipine, pindolol, verapamil	6 primary outcomes: Nonfatal stroke or death from cerebrovascular disease; nonfatal MI or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; total major cardiovascular events (stroke, CHD events, heart failure, and other cardiovascular death); total cardiovascular death; total mortality	27 RCTs included. Total major cardiovascular events were reduced to a "comparable extent" in patients with and without DM for ACE-I, calcium antagonists, ARBs, diuretics, and beta-blockers (p> 0.19 for all by x2 test of homogeneity) Stroke: ARBs provided less protection for those with DM, than for those without DM (p=0.05) CHD: ARBs provided greater protection for those with diabetes than for those without diabetes (p=0.002). Reduction in risk of total major cardiovascular events (p=0.03) and cardiovascular deaths (p=0.02) in those with DM vs without DM using regimens targeting lower BP goals (favors more vs less intensive regimen). More protection against cardiovascular death (p=0.05) and total mortality (p=0.03) for those with DM vs without DM using ACE-I	NR
Costa et al, 2006[119] *Good*	RCT Lipid lowering drug treatment: lovastatin, pravastatin, gemfibrozil, atorvastatin, simvastatin, fluvastatin, lovastatin	Primary outcomes: Major coronary events (coronary artery disease death, non-fatal MI) or myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) Secondary outcomes: Coronary artery disease death, non-fatal MI, revascularization procedures, stroke, blood lipid concentration changes, TC, LDL, HDL,TG	12 studies included (6 primary prevention, 8 secondary prevention) Lipid lowering drug treatment was found to be equally efficacious in DM and nonDM patients: Primary Prevention: RR for major coronary events treated with either statins or gemfibrozil: DM: 21% (95% CI, 11-30%, p<0.0001) NonDM: 23% (95% CI, 12-33%, p=0.0003) [I^2 = 68%] RD for major coronary events: DM: -0.02 (-0.04 to -0.00; p=0.1) NonDM: -0.02 (-0.02 to -0.01; p<0.00001) NNT for major coronary events: DM: 37 (24 - 75) NonDM: 47 (35 - 73)	NR

HPS, Heart Protection Study; IDNT, Irbesartan Diabetic Nephropathy Trial; LDL, low density lipoprotein; LIFE, Losartan Intervention for Endpoint Reduction Trial; MI, myocardial infarction; NICOLE, Nisoldipine In Coronary Artery Disease in Leuven; NNT, number needed to treat; NR; not reported; PART2, Prevention of Atherosclerosis with Ramipril Therapy; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk trial; RCT, randomized controlled trial; RENAAL, Randomized Evaluation of Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; RD, risk difference; RR, relative risk; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial; SCOPE, Study on Cognition and Prognosis in the Elderly; SYST-EUR, Systolic Hypertension-Europe trial; TC, total cholesterol; TG, triglycerides; UKPDS-HDS, United Kingdom Prospective Diabetes Study; y, year.

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name **Author, year** (in date order)	**Objective**	**Type of screening;** **Perspective**	**Type of model**	**Population** **Country**	**Included costs**	**Discount rate**
Global Diabetes Model Brown et al, 2000[133, 126]	To examine the predictions of the Global Diabetes Model for 20y cumulative rates of various outcomes	NA Payer	Monte Carlo microsimulation (stochastic) model using continuous prediction equations; can be used to simulate a single individual or populations	5000 newly diagnosed DM2 white males; no CVD or other macro- or microvascular complications; based on Kaiser health maintenance organization United States	Direct medical costs	0%
CDC / RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* CDC Diabetes Group, 2002[123]	To estimate the incremental CE of intensive glycemic control, intensified HT control, and reduction in TC for patients with DM2	Health care system (for costs)	Markov model, with emphasis on macrovascular complications, interdependencies among diabetes progression paths Subjects proceed through 5 different disease paths; nethropathy, neuropathy, retinopathy, CHD, stroke	Newly diagnosed DM2; 55% female, 8% 25-34y, 8% 35-44y, 26% 45-54y, 18% 55-64y, 23% 65-74y, 13% 75-84, 4% 84-94y United States	Health care system only; no indirect or direct patient costs	Costs and QALYs discounted at 3% (sensitivity analysis 0 to 5%)
CORE Model (*Center for Outcomes Research)* Palmer et al, 2004[124, 128]	To simulate the development of diabetes complications and the effect of new and existing interventions on clinical and cost outcomes	Third party payer	Markov using Monte Carlo simulation; 15 submodels each of which simulates different complications associated with DM	Newly diagnosed patients: baseline age 52y, A1c 9.1%, SBP 137 mm Hg, TC 212 mg/dl, HDL 39 mg/dl Switzerland; modeled using payer US costs United States	Direct medical costs; day-to-day DM management costs excluded; expressed in 2003 values in the US setting	3% annual rate for costs; outcomes not discounted

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name **Author, year** (in date order)	**Base case assumptions**	**Time horizon**	**Data sources**	**Sensitivity analyses**
Global Diabetes Model Brown et al, 2000[133, 126]	A1c predicts microvascular events only; risks maintained at baseline levels	20y	Kaiser databases, world scientific literature, observational data such as Framingham Heart Study	None (Palmer 2000)
CDC / RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* CDC Diabetes Group, 2002[123]	Intensified HT control did not have an effect on CHD; intensive treatments assumed for lifetime	Death or age 95y	UKPDS for population distribution at diagnosis, other data for DM and CHD progression from other sources; costs data from literature; health utility values: 0 deceased, 1 perfect health, 0.690 blindness, lower extremity amputation 0.80; estimates of hazard rates of complications based on DCCT data and assumed to work for DM2; efficacy of intensified HT treatment from UKPDS; estimates of risk reduction from reduction in cholesterol on CHD (31% in subjects without CHD, 25% in subjects with CHD) based on West of Scotland Prevention Study	If intensive glycemic control reduced CHD risk, QALYs increased to 0.3325 and CE ratio decreased to $27000 If microalbuminuria does not lead to HT or persons with HT do not progress faster: moderate increase in CE ratio Intervention provided to subjects who develop HT after diagnosis of DM2: CE ratio $2091/QALY Reduction in TC: if intervention required no additional visits or tests: decreased CE ratio by $47716/QALY
CORE Model (*Center for Outcomes Research)* Palmer et al, 2004[124, 128]	Rates of MI for males and females are the same; most transition probabilities can be altered	Lifetime; 1 to 90y can be modeled	UKPDS, Framingham, other published sources	Discount rate 0-6%: no impact on relative outcomes

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name **Author, year** (in date order)	**Intervention**	**Outcomes**	**Conclusions**
Global Diabetes Model Brown et al, 2000[133, 126]	Intensive lipid management (LDL from 150 to 100 mg/dl and HDL from 40 to 50 mg/dl)	A1c 9.5%, SBP 130: % survival: 82.7% Total costs per person ($US): $85,920 Lower costs for lower A1c, higher costs for higher SBP	Survival improves with intensive lipid therapy
CDC / RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* CDC Diabetes Group, 2002[123]	All subjects were assumed to receive conventional treatment to control blood glucose (treatment based on UKPDS control arm which produced an average A1c of 7.9% over 10y) Intensive glycemic control: to reduce FPG to <108 mg/dl using chlorpropamide, glipizide, insulin Intensified HT control: ACE-I or B-blocker for baseline BP ≥ 160/95 Reduction in TC: pravastatin for baseline level ≥200 mg/dl	Intensive glycemic control applied to all persons newly diagnosed with DM2 in the US: increase in QALY of 0.1915 (discounted), CE ratio: $41,384 per QALY; CE ratio increases markedly with age; cumulate incidence of nethropathy, neuropathy, retinopathy decreased by 11 to 27% Intensified HT control: increased QALYs by 0.392 relative to moderate HT control; CE ratio - $1,959/QALY (i.e. cost savings); age had little effect Reduction in serum cholesterol: increase in discounted QALYs 0.3475, CE ratio $51,889 per QALY, lowest ratio for 45-85y	Intensified HT control reduces costs and improved health outcomes relative to moderate HT control (CE ratio - $1959); intensive glycemic control (CE ratio $41,384) and reduction in serum cholesterol (CE ratio $51,889) increase costs and improve health outcomes Intensive glycemic control is most CE for younger persons
CORE Model (*Center for Outcomes Research)* Palmer et al, 2004[124, 128]	Hypothetical interventions that led to individual 10% improvements in A1c, SBP, TC, HDL	QALE: increased 1.72y with improvements in all of A1c, SBP, TC, HDL Lifetime costs of DM-related complications: decreased $14,533 with improvements in all of A1c, SBP, TC, HDL; improved A1c alone: decreased $10,800, SBP alone: decreased $7,048	10% improvements in A1c, SBP, TC, HDL, individually and in combination are likely to improve length and quality of life; most marked improvement with all 4; individually A1c had greatest gains in life expectancy and quality-adjusted life expectancy

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name Author, year (in date order)	Objective	Type of screening; Perspective	Type of model	Population Country	Included costs	Discount rate
UKPDS Model (*United Kingdom Prospective Diabetes Study)* Clarke et al, 2005,[125] 2004,[131] 2003,[130] 2001[129]	To estimate the economic efficiency of: 1) Intensive BG and BP control in DM2 patients with HT 2) Metformin in overweight patients	Health care purchaser	UKPDS Outcomes Model: based on an integrated system of parametric equations which predict probability of endpoints and Monte Carlo methods to predict occurrence of events; probabilistic discrete-time illness-death model	Newly diagnosed DM2 aged 25-65y; mean age 52.4y, 58% male; 81% Caucasian; n=3867 United Kingdom	Direct medical costs	3.50%

Abbreviations: ACE-I, angiotension converting enzyme inhibitor; BG, blood glucose; BP, blood pressure; CE, cost effectiveness; CHD, coronary heart disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DM, diabetes; DM2, type 2 diabetes; FPG, fasting plasma glucose; HDL, high density lipoprotein; HT, hypertension; LDL, low density lipoprotein; MI, myocardial infarction; N, number of participants; NA, Not applicable; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; SBP, systolic blood pressure; TC, total cholesterol; UKPDS, United Kingdom Prospective Diabetes Study; US, United States; y, year

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name **Author, year** (in date order)	**Base case assumptions**	**Time horizon**	**Data sources**	**Sensitivity analyses**
UKPDS Model (*United Kingdom Prospective Diabetes Study)* Clarke et al, 2005,[125] 2004,[131] 2003,[130] 2001[129]	UKPDS data and costs used; end-of-trial A1c and BP levels same for all patients (mean); i.e. assumes no continuing benefit of therapy	Lifetime (Clarke 2005) Within-trial data: mean duration 10.3y (Clarke 2003)	UKPDS for both outcomes and costs	Various

APPENDIX B8. STUDIES MODELING TREATMENT OF PERSONS WITH NEWLY-DIAGNOSED TYPE 2 DIABETES

Model name **Author, year** (in date order)	**Intervention**	**Outcomes**	**Conclusions**
UKPDS Model (*United Kingdom Prospective Diabetes Study)* Clarke et al, 2005,[125] 2004,[131] 2003,[130] 2001[129]	Intensive BG control with insulin or sulphonylurea versus conventional glucose control (mainly diet); 342 patients >120% of ideal body weight were assigned to metformin and compared with 411 overweight patients on conventional treatment Embedded study randomized 1148 patients with HT to BP<180/<105 vs n=758 with BP goal <150/85 mm Hg	QALY per patient modeled over lifetime: Intensive BG control: 0.15(-0.20, 0.49) Metformin therapy: 0.55(-0.10, 1.20) Tight BP control: 0.29(-0.14, 0.59) Probability of being cost-effective at a ceiling ratio of 20,000 Pounds per QALY: Intensive BG control: 74% Metformin therapy: 98% Tight BP control: 86% Life years gained per patient with metformin treatment versus conventional, within-trial data (Clarke 2001): 0.6 (95% CI, 0.0, 1.2)	Intensive BG control and BP control for persons with HT adds QALYs over lifetime; relatively cost-effective compared to many other accepted uses of health care resources

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Country Setting Year(s)	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection
Diabetes Prevention Program DPP Research Group, 2002,[79] 2000,[139] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	US 27 centers 1996 - 1999	I1: 1079 I2: 1073 C: 1082	2.8y (mean) (range, 1.8 to 4.6) For CVD outcomes: 3.2y (DPP 2005)	High risk for DM2: ≥ 25y, BMI ≥ 24 kg/m^2 (≥ 22kg/m^2 Asian American) FG of 95-125 mg/dl (5.3 - 6.9 mmol/l) (or ≤124 mg/dl for American Indian) and OGTT (2 hr-75-g) 140-199 mg/dl (7.8 to 11.0 mmol/l)	Recent MI, CHD symptoms, taking medication for glucose intolerance, serious illness	Volunteers, 4-step screening process including 3w run-in with trial of medication compliance
DREAM (*Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)* DREAM Trial Investigators, 2004,[147] 2006[82, 148] *Good*	21 countries (191 clinical sites) Screened between July 2001 - August 2003	I: 2365 C: 2634	3y (median)	Age ≥30y IFG: FPG ≥110 and <126 mg/dl (≥6.1 mmol/l and <7.0 mmol/l) and a 2-h plasma glucose <200 mg/dl (<11.1 mmol/l) after a 75-g OGTT; or IGT: FPG <126 mg/dl (<7.0 mmol/l) and 2-h plasma glucose ≥140 and <200 mg/dl (≥7.8 mmol/l and <11.1 mmol/l) [revised criteria in 2003 to include isolated IFG 110 to <126 mg/dl (6.1 to <7.0 mmol/l) and 2-h plasma glucose <140 mg/dl (<7.8 mmol/l)]	Current use of ACE-I and/or thiazolidinediones or the inability to discontinue; previous ischaemic CVD or uncontrolled hypertension requiring medication, history of diabetes, renal or hepatic disease, major illness, use of experimental drug, pregnant, psychiatric disorder, disease or meds that affect glucose tolerance, substance use	Community recruitment, wide variety of strategies that varied by site and country (advertising, news reports, screening fairs, mailings, referral from physicians, etc.); 24,872 screened, 5268 randomized

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Population	Existing vascular disease	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood Pressure (mm Hg)
Diabetes Prevention Program DPP Research Group, 2002,[79] 2000,[139] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	Race overall: Caucasian (55%); African American (20%); Hispanic (16%); American Indian (5%); Asian American (4%) Age y (SD): I1: 50.6 (11.3); I2: 50.9 (10.3); C: 50.3 (10.4) % male: I1: 32; I2: 33.8; C: 31	Overall (%): History of MI: 32 History of stroke: 34 History of revascularization: 16 Metabolic syndrome: 53 (3 or more criteria from the National Cholesterol Education Program Adult Treatment Panel III)	FPG (mg/dl) (SD) I1: 106.3 (8.1) I2: 106.5 (8.5) C: 106.7 (8.4) A1c I1: 5.91 (0.51) I2: 5.91 (0.50) C: 5.91 (0.50) % Family history DM2 I1: 69.8 I2: 68.3 C: 70.1	Overall: Elevated LDL (or taking medications): 44% Elevated TG (or taking medication): 28.8%	DBP (SD): I1: 78.6 (9.2) I2: 78.3 (9.5) C: 78.0 (9.2) SBP (SD): I1: 123.7 (14.8) I2: 124.0 (14.9) C: 123.5 (14.4) Overall HTN: 29.6%
DREAM (*Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)* DREAM Trial Investigators, 2004,[147] 2006[82, 148] *Good*	Geographic distribution (%): I: North America (41.1), South America (21.4), Europe (20.8), India (12.5), Australia (4.2) C: North America (40.5), South America (21.7), Europe (21.1), India (12.6), Australia (4.1) Age y (SD): I: 54.6 (10.9); C: 54.8 (10.9) % male: I: 41.7; C: 39.9 Isolated IGT (%): 57 Isolated IFG (%): 14 Both IGT and IFG (%): 29	None (excluded)	FPG (SD): I: 140 [5.8 mmol/l (0.7)] C:104 [5.8 mmol/l (0.7)] A1c (%): NR	Statin or fibrate: I: 14.8%; C: 14.8%	DBP (SD): I: 83.3 (10.6); C: 83.5 (10.9) SBP (SD): I: 135.9 (17.9); C: 136.3 (18.8) HTN history: I: 44%; C: 43%

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Other CVD risk factors**	**Intervention**	**Primary endpoint(s)**
Diabetes Prevention Program DPP Research Group, 2002,[79] 2000,[139] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	BMI (kg/m2) (SD): I1: 33.9 (6.8) I2: 33.9 (6.6) C: 34.2 (6.7) Weight (kg) (SD): I1: 94.1 (20.8) I2: 94.3 (19.9) C: 94.3 (20.2) Waist circumference (cm) (SD): I1: 105.1 (14.8) I2: 104.9 (14.4) C: 105.2 (14.3) Waist-to-hip ratio (SD): I1: 0.92 (0.08) I2: 0.93 (0.09) C: 0.93 (0.09)	All participants encouraged to follow Food Guide Pyramid and a National Cholesterol Education Program Step 1 diet (referred to as standard lifestyle intervention) I1: Lifestyle/dietary changes: intensive 24w program, 16 lesson curriculum, attain and maintain ≥ 7% weight loss, physical activity 150 min/w I2: Metformin: 850 mg qd for 1m, then bid, standard lifestyle recommendations (written form and 20 min one-on-one session annually) C: Placebo bid, standard lifestyle recommendations	Progression to DM2; CVD and risk factors, changes in glycemia, insulin secretion, obesity, PA, diet, QOL, AEs
DREAM (*Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)* DREAM Trial Investigators, 2004,[147] 2006[82, 148] *Good*	Weight (kg) (SD): I: 84.8 (19); C: 85 (18.9) BMI (kg/m^2) (SD): I: 30.8 (5.6); 31 (5.6) Waist-to-hip ratio (men;women) (SD): I: 0.96 (0.07); 0.86 (0.07); C: 0.96 (0.07); 0.87 (0.09) Waist circumference (cm) (men;women) (SD): I: 101 (14); 96 (14); C: 102 (13); 96 (14) Current or former tobacco use: I: 43.9%; C: 45.3%	C: matching placebo I: 4 mg qd rosiglitazone for 2m, then 8 mg qd Also randomized to ramipril 15mg qd or placebo on 2x2 factorial design	Primary endpoint: composite of incidence of diabetes and death; Secondary outcomes included CV events, renal events, changes in glucose tolerance and other measures of beta cell functions

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Outcomes	Adherence Withdrawals (%)
Diabetes Prevention Program DPP Research Group, 2002,[79] 2000,[139] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	Crude incidence DM2 [cases per 100 person y]: C: 11; I2: 7.8; I1:4.8 (p <0.001) Incidence of DM2 was 58% lower (95% CI, 48-66%) for I1 and 31% lower (95% CI, 17-43) for I2 than placebo group (p< 0.05) Cumulative incidence DM2 at 3y (%): C: 28.9; I2: 21.7; I1: 14.4% NNT for 3y to prevent 1 case of DM2: I1 6.9 (95% CI, 5.4 - 9,5); I2 13.9 (95% CI, 8.7 - 33.9) Cumulative incidence of CVD and event rate: NSD among groups, but the few CVD events did not provide adequate statistical power (DPP 2005) Prevalence of HTN at 3y: I1 23%, I2 32%, C 31% (between-group p-value <0.04) Subgroup analyses (*post hoc*): NSD among treatments for sex, race Intervention more effective among persons with lower BG at baseline; metformin more effective with increased BMI Lifestyle group: achieved goal of ≥ 7% weight loss at most recent visit: 38%; 150 min/w of activity: 58% Average weight loss (kg): I1 5.6, I2 2.1, P 0.1 Large waist circumference at baseline was a predictor of diabetes in the placebo and lifestyle groups (Cox hazard ratio per 1 SD in placebo and lifestyle 1.43 and 1.49 for men and 1.29 and 1.53 for women) Lifestyle intervention was more effective in decreasing diabetes incidence with increasing age (p=0.007); metformin group showed trend toward higher diabetes incidence in older participants (p=0.07) DPP women and men were less inactive than the NHANES III sample for most age, BMI and rate/ethnic groups	Medication adherence: I2: 77%; C: 72% (P <0.001) 97% were given full dose of pills, 3% only 1 tablet qd to reduce side effects I1: 50% achieved weight loss of 7% or more at the end of the 24w curriculum period, 38% at the most recent visit; 74% did at least 150 min of activity per week at 24w, 58% at most recent visit I1: Dietary change/daily energy intake kcal decreased (mean/SD) of 450/26; I2: 296/23; C: 249/27)
DREAM (*Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)* DREAM Trial Investigators, 2004,[147] 2006[82, 148] *Good*	Rosiglitazone: New onset DM2 or death: HR: 0.40, 95% CI 0.35-0.46; P<0.0001; Deaths: HR; 0.91, 95% CI, 0.55-1.49; p=0.7 New onset DM2: HR 0.38 (95% CI, 0.33 - 0.44), p<0.0001 Rates of progression to diabetes: I: 280 (10.6%) vs. C: 658 (25%) (p< 0.0001) Both groups had similar frequency of the composite cardiovascular outcome (myocardial infarction, stroke, cardiovascular death, new angina, revascularization, hypertension) and all but one of the components of the composite; Heart failure: HR 7.03 (95% CI, 1.60 - 30.9), p=0.01 Ramapril: New onset DM2 or death: HR: 0.91 (95% CI, 0.81 - 1.03), p=0.15 New onset DM2: HR: 0.91 (95% CI, 0.80 - 1.03) CV events: NSD between groups	Stopped drug on or before last visit: I: 654; C: 566 <u>Reasons for stopping:</u> Patient refusal: I: 18.9%; C: 16.7% Edema: I: 4.8%; C: 1.6% Physician's advice: I: 1.9%; C: 1.5% Weight gain: I: 1.9%; C: .6% Hypoglycemia: I: 1, C: 3 Total lost to follow-up: I: 772; C: 601 % adherent at the end of the study: I: 71.6, C: 75.1 I: 28.5%; C: 24.3% stopped taking pills at any time I: 23.6%; C: 20.2% were not taking pills at their last visit

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Adverse Events**	**Other Results**
Diabetes Prevention Program DPP Research Group, 2002,[79] 2000,[139] 2005[140, 145] Fujimoto et al, 2000[141] *Good*	GI symptoms (no. per 100/person-y): I1: 12.9* I2: 77.8* C: 30.7 Musculoskeletal symptoms (no. per 100/person-y): I1: 24.1* I2: 20 C: 21.1 Hospitalization (%): I1: 15.6 I2: 8.4 C: 7.9 Death (no. per 100/person-y): I1: 0.10 I2: 0.20 C: 0.16 *p<0.0167 compared to control	
DREAM (*Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)* DREAM Trial Investigators, 2004,[147] 2006[82, 148] *Good*	Peripheral edema at final visit: I: 6.8%; C: 4.9% (p=0.003)	Effects of rosiglitazone were the same in all regions of the world, different ethnic groups, in both sexes, and across all ages Every 1000 people treated with rosiglitazone for 3y, 144 cases of diabetes will be prevented, with an excess of 4-5 cases of congestive heart failure

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Country Setting Year(s)	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection
Finnish Study Tuomilehto et al, 2001[138] Lindstrom et al, 2006,[153] 2003,[149, 150] Eriksson et al, 1999[151] Laaksonen et al, 2005[152] *Fair*	Finland 5 primary care centers November 1993 - June 1998	I: 265 C: 257	3.2y (mean) Lindstrom 2006: Post - intervention 3y (median); total follow-up 7y (median); Intervention discontinued after 4y (median)	Ages 40-65y; BMI >25 kg/m^2 IGT: plasma glucose concentration of 140 to 200 mg/dl (7.8 to 11.0 mmol/l) 2-h after 75 g of glucose (FPG <140 mg/dl)	DM2, chronic disease, psychological or physical disabilities	Screening members of high risk groups (e.g. 1st degree relatives of patients with DM2 and opportunistic screening)
Heymsfield et al, 2000[80] *Fair-poor*	US and Europe 39 clinical research centers 1992 - 1995	I: Lifestyle/orlistat 359 C: Lifestyle only 316	2y (attained by 69% of each of C and I group)	Age >18y, BMI of 30-42, adequate contraception in women of childbearing years, absence of weight loss (>4kg) in the previous 3m IGT: 2-h BG 140 to 198 mg/dl (7.8 to 11.0 mmol/L); diabetes: 2-h BG > 198 mg/dl(>11.0 mmol/l)	Had stopped smoking in the last 6m, significant cardiac, renal, hepatic, gastrointestinal, psychiatric, or endocrine disorders; drug treated DM2, history or presence of substance abuse, excessive intake of alcohol, or used medications that alter appetite or lipid levels	Run-in period used to stratify by capacity to lose weight

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Population**	**Existing vascular disease**	**FBG (mg/dl)** **A1c (%)**	**Lipids (mg/dl)**	**Blood Pressure (mm Hg)**
Finnish Study Tuomilehto et al, 2001[138] Lindstrom et al, 2006,[153] 2003,[149, 150] Eriksson et al, 1999[151] Laaksonen et al, 2005[152] *Fair*	Race: NR Age y (SD): I: 55 (7); C: 55 (7) % male: I: 34.34 C: 31.52	NR	FPG (mg/dl) (SD): I: 109 (14); C: 110 (13) A1c (SD): I: 5.7 (0.6); C: 5.6 (0.6)	TC (SD): I: 215 (37); C: 215 (35) HDL (SD): I: 46 (12): C: 47 (11) TG (SD): I: 154 (72); C: 158 (69) % on lipid meds: I: 5%; C: 7%	DBP (SD): I: 86 (9); C: 86 (10) SBP (SD): I: 140 (18); C:136 (17) % on anti-HTN meds: I: 29%; C: 31%
Heymsfield et al, 2000[80] *Fair-poor*	Age: 43.9y Weight: I: 99.8 kg, C: 99.0	None existing	I: 109 (6.04 mmol/l) C: 107 (5.92 mmol/l)	Varied among the 3 studies	Varied among the 3 studies

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Other CVD risk factors	Intervention	Primary endpoint(s)
Finnish Study Tuomilehto et al, 2001[138] Lindstrom et al, 2006,[153] 2003,[149, 150] Eriksson et al, 1999[151] Laaksonen et al, 2005[152] *Fair*	BMI (SD): I: 31.3 (4.6); C: 31 (4.5) Waist circumference (cm) (SD): I: 102 (11); C: 100.5 (10.9) Hip (cm) (SD): I: 110.4 (10.5); C; 109.4 (9.7)	C: 2-page leaflet and oral discussion on diet and exercise at baseline and annual visits; 3d food diary at baseline and annual visits I: 7 nutritionist sessions in y 1 then 1 session every 3m; 3-day food diary 4 times a y; detailed tailored advice on goals; individual counseling; supervised resistance training; nutrient intakes computed; decrease weight 5+%, fat intake <30% total calories, increase fiber, exercise 30 min qd	Progression to diabetes Secondary endpoints: Weight loss, BMI, waist, FPG, A1c, TC, HDL, TG Lindstrom 2006: Incidence of DM2 at 7y follow-up
Heymsfield et al, 2000[80] *Fair-poor*	NR	All subjects: 1. Diet: 30% of calories from fat for 4w run-in period, 2. Exercise: Y 1: energy intake was prescribed for each patient based on an estimated daily maintenance energy requirement formula, Y 2: weight maintaining diet/exercise regimen Drug: I: Orlistat 120 mg tid 52 or 104w; C: placebo tid	Weight loss

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Outcomes	Adherence Withdrawals (%)
Finnish Study Tuomilehto et al, 2001[138] Lindstrom et al, 2006,[153] 2003,[149, 150] Eriksson et al, 1999[151] Laaksonen et al, 2005[152] *Fair*	Cumulative incidence DM2 58% lower in I than in C: HR: 04; 95 % CI, 0.3 to 0.7; p<0.001) at Y6 Cumulative incidence DM2: number (%): Y1: I: 5 (1.9); C: 16 (6.1) Y2: I:15 (6.3); C: 37 (14.4) Y3: I: 22 (9.1); C: 51 (20.9) (p=0.0001) Y4: I: 24 (10.9); C; 53 (23) Y5: I: 27 (20); C: 57 (34.4) Y6: I: 27 (20); C: 59 (42.6) Absolute incidence DM2 (per 100 person-y): I: 32, C:78 DM2 diagnosed in 86 subjects; I: 27; C: 59; Absolute incidence of DM2 in I: 32/1000; C: 78/1000 For men, incidence of diabetes was reduced by 63% (95% CI, 18 to 79%; P= 0.01) and in women by 54% (95% CI, 26 to 81%; p= 0.008) 22 subjects with IGT can be treated for 1y with this intervention, or 5 subjects for 5y, to prevent one case of diabetes. Laakensen 2005: After adjusting for other variables, subjects in the upper 1/3 of the change in total LTPA were 80% less likely to develop diabetes than those in the lower 1.3 (RR 0.20, 95% CI 01.-0.41; P < 0.001) Lindstrom 2006: Incidence rate 7y follow-up: 4.3 (95% CI 3.4 -5.4) and 7.4 (95% CI 6.1 -8.9) per 100 person y in the I and C group, respectively (p=0.0001 log rank test); HR 0.57(0.43-0.76) Incidence rates during the 3y post-intervention period: I: 4.6 and C: 7.2 (p=0.0401) (=36% reduction in relative risk) Cumulative incidence of DM2 at Y6 was 23% in the I group and 38% in the C group [ARR of 15% (7.2 - 23.2)]. NNT to prevent one case of DM2 by lifestyle intervention = 22 for 1y	Rate of adherence to exercise portion of I ranged from 50-85% in different centers Withdrawals (number): I: 23; C: 17 (9 could not be contacted, 3 severe illness, 1 died, 27 for personal reasons) Lindstrom 2006: Follow-up 7y: loss to follow-up I: 10%, C: 8% (p=0.362)
Heymsfield et al, 2000[80] *Fair-poor*	Change in OGTT status at end of the study: (%) (from Heymsfield) IGT at baseline: normal I 71.8%, C 49.1%; IGT: I 25.4%, C 43.4%; DM2: I 3.0%, C 7.6%; p=0.04 between groups Normal at baseline: normal I 93.4%, C 88.0%	Completers: I: 246/333; C: 217/281 (NSD)

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Adverse Events	Other Results
Finnish Study Tuomilehto et al, 2001[138] Lindstrom et al, 2006,[153] 2003,[149, 150] Eriksson et al, 1999[151] Laaksonen et al, 2005[152] *Fair*	NR	
Heymsfield et al, 2000[80] *Fair-poor*	Sjostrom: overall AEs: I 94%, C 82% GI effects more common with I and generally short duration Serious AEs: I 25, C 24	Weight change

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Country Setting Year(s)	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	India March 2001 - July 2002	C-1: 136 I-2 (lifestyle modification): 133 I-3 (metformin): 133 I-4 (lifestyle and metformin): 129	3y	IGT (WHO criteria): (FG <126 mg/dl [<7.0 mmol/l]; 2-hr glucose 140-199 mg/dl [7.8-11.0 mmol/l]; 35-55y	Major illness; diabetes	Community-based: middle class, workplace service organizations, advertisement for volunteers 10,839 screened, 12.3% had IGT of those, 77% had OGTT
Kosaka et al, 2005[81] *Fair*	Japan, Toranomon Health Medical Center , Hospital 1990 - 1992	I: 102 C: 356	4y	30-69y IGT: FPG (mg/dl): <140 and a 2-h PG (2hPG) value of 160-239 on 100-g OGTT	Previous history of diabetes; diagnosed or suspected neoplasm, disease of the liver pancreas, endocrine organs or kidney; history of ischemic heart disease or cerebrovascular disease	Health screening program for government employees
Pan et al, 2003[156] *Fair*	China 15 medical centers	I: 126 C: 132	16w	IGT (WHO criteria): 2 h-postprandial plasma glucose $\geq$140 mg/dl, <200 mg/dl and FPG <125 mg/dl; age 35-70y, BMI >19 and $\leq$34kg/m^2	Pregnant or lactating women, DM2, childbearing age with no contraception, major diseases, major CV event in last 6m, medication that would impair intestinal mobility, other medications within the last 3m, certain BP and TG parameters, emotional disorder or substance abuse treatment within the last 30d, HTN	Methods of recruitment NR

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Population	Existing vascular disease	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood Pressure (mm Hg)
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	Race: Asian Indian Age y (SD): C: 45.2 (5.7); I-2: 46.1 (5.7); I-3: 45.9 (5.9); I-4: 46.3 (5.7) % male: C: 76%; I-2: 78%; I-3: 80%; I-4: 81%	None (major illness excluded)	FPG (SD): C: 99 [5.5 mmol/l (0.8)] I-2: 97 [5.4 mmol/l (0.7)] I-3: 97 [5.4 mmol/l (0.8)] I-4: 97 [5.4 mmol/l (0.8)] A1c (SD): C-1: 6.2 (0.5) I-2: 6.1 (0.5) I-3: 6.2 (0.6) I-4: 6.2 (0.6)	TC (SD): C: 197 [5.1 mmol/l (0.9)] I-2: 201 [5.2 mmol/l (0.9)] I-3: 201 [5.2 mmol/l (1.0)] I-4:197 [5.1 mmol/l (0.9)] TG: C-1: 168 [1.9 mmol/l (1.2)] I-2: 177 [2.0 mmol/l (1.4)] I-3: 150 [1.7 mmol/l (0.9)] I-4: 150 [1.8 mmol/l(0.9)] % on lipid meds: NR	DBP (SD): C-1: 76.2 (8.6) I-2: 74.4 (8.1) I-3: 74.4 (9.2) I-4: 74.9 (8.1) SBP (SD): C-1: 124.1 (16) I-2: 121.5 (14.4) I-3: 120.7 (15.9 I-4: 122.4 (14.3) % on anti-HTN meds: NR % with HTN: Table 1
Kosaka et al, 2005[81] *Fair*	Race: Japanese Age y: In 50's: I: 56.9%; C:53.9% % male: 100	None	FPG (mg/dl) (SD): I: 113 (7.6) C: 112 (8.5) A1c (%): NR	TC (SD): I: 213 (42); C: 214 (38) HDL (SD): I: 52 (14); C: 51 (13) TG (SD): I: 137 (88); C: 138 (78) % on lipid meds: NR	SBP (SD): C: 124 (17) I: 123 (18) DBP (SD): C: 79 (11) I: 78 (13)
Pan et al, 2003[156] *Fair*	Race: Chinese Age y (SD): I:53.4 (8.63); C: 55.6 (8.31) (between-group p=0.034) % male: I: 39.2; C: 40.9	NR; excluded those with major cardiovascular events in the last 6m	Maximum PP plasma glucose (mg/dl) (SD) I : 185.5 (35.5); C: 187.3 (29.7) A1c (%): I: 6.51 (0.72), C: 6.61 (0.62)	TC (SD): I: 199.1 (40.2); C: 201.8 (42.8) LDL (SD): I: 120.9 (33.9); C: 122.4 (34.4) HDL (SD): I: 53.6 (13.2); C: 53 (11.6) TG (SD): I: 138.2 (77.3); C: 144.6 (68.1) % on lipid meds: NR	DBP (SD): I: 78 (7.8); C: 78.1 (8.4) SBP (SD): I: 125.4 (14.1); C: 126.8 (14.9) % on anti-HTN meds: NR

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Other CVD risk factors**	**Intervention**	**Primary endpoint(s)**
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	Smokers (%) (SD): C: 36 (26.5) I-2: 29 (21.8) I-3: 23 (17.3) I-4: 27 (20.9) BMI (kg/m^2) (SD): C-1: 26.3 (3.7) I-2: 25.7 (3.3) I-3: 25.6 (3.7) I-4: 25.6 (3.3)	C: Placebo I-2: LSM; advice on healthy diet and regular physical activity at first visit and by phone or letter after 2w; personal motivation phone calls every m; in-person sessions every 6m I-3: Metformin 250 mg bid I-4: LSM plus Metformin	Incidence of DM2 (FBG ≥ 126 mg/dl and/or 2-h PG ≥ 200, confirmed by OGTT)
Kosaka et al, 2005[81] *Fair*	BMI (kg/m^2) (SD): I: 24 (2.3) C: 23.8 (2.1) Family history of DM: I: 41.2 % C: 42.4 %	C: At start and every 6m visit: BMI >24kg/m^2: advised to take 5-10% smaller meals, increase PA BMI <24kg/m^2: at start and every 6m, advised to not gain weight by dieting and to keep up PA I: At start and every 3-4m visit: BMI $\geq$ 22 kg/m2: informed of desirable body weight, advised to weigh themselves weekly, decrease food by 10%, increase vegetables, increase PA to 30-40 mins qd BMI < 22Kg/m^2: advised to maintain their present weight and not gain weight Review of current eating patterns, diet advice, alcohol consumption, eating out, and PA were provided	Primary outcome: Incidence of DM2, FPG Secondary outcome: A1c, body weight, BMI
Pan et al, 2003[156] *Fair*	Weight (kg) (SD): I: 67.5 (10.4); C: 68.0 (11.6)	I: acarbose 50 mg qd for 1 w, 50 mg bid for 2 w, 50 mg tid to 16w C: Placebo	Primary outcome: PPGe, serum insulin profile, postprandial glucose profile Secondary outcome: maximum PP insulin concentration, lipid profile, blood pressure, A1c, body weight, conversion to DM2

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Outcomes	Adherence Withdrawals (%)
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	Cumulative incidence of DM2 at Y3 C-1: 55% I-2: 39.3% I-3: 40.5% I-4: 39.5% The NNT for 3y to prevent one case of DM2: I-2: 6.4 I-3: 6.9 I-4: 6.5 ARR in DM2 (%): I-1 (15.7), I-2 (14.5), I-3 (15.5) RRR (%, 98% CI): I-1 28.5 (20.5, 37.3), I-2 26.4 (19.1, 35.1), I-3 28.2 (20.3, 37.0)	Overall completion rate: 95.1 C: 98.5 I-2: 91 I-3: 96 I-4: 94.6
Kosaka et al, 2005[81] *Fair*	Cumulative incidence of diabetes in the intervention group during the 4y I (3%) vs. C (9.3%) (between-group p=0.043). (67.4%) Reduction in diabetes in I group	% of participants who completed 4y follow-up: C: 91%; I: 93.1%
Pan et al, 2003[156] *Fair*	Incidence of diabetes I: 7 subjects (5.6%); C: 12 subjects (9.5%); between-group p=0.245	Compliance: I: 98.4%; C: 95.5% Withdrawals (number): I: 2, C: 3

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Adverse Events**	**Other Results**
Indian Diabetes Prevention Programme Ramachandran et al, 2006[154] *Fair*	Cardiovascular events (no. of events): C: 2 I-2: 4 I-3: 0 I-4: 5 Death: C-1: post surgery (cerebrovascular accident) I-2: hepatic encephalopathy I-4: post thyroid surgery Symptoms of hypoglycemia: reported when the metformin dose was briefly at 500 mg bid Symptoms did not occur when reduced to 250 mg bid	See paper for details
Kosaka et al, 2005[81] *Fair*	NR	The incidence of diabetes was significantly higher in those with higher baseline FPG (11.8%) than in those with lower FPG (5.4% p=0.044)
Pan et al, 2003[156] *Fair*	Overall drug-related AEs: I: 35.7%; C: 18.2% (differences mainly due to GI effects) Flatulence: I; 15.9%; C: 6.1%; Abdomen enlarged I: 13.5%; C: 3.8% Diarrhea: I: 9.5%; C: 2.3% Serious AEs: I: 1 cerebral infarction, 1 hepatitis, 1 glaucoma C: 1 tenosynovitis	I group showed significant reductions in PPG, serum insulin concentrations, and body weight when compared to placebo TG was the only lipid parameter to be reduced by intervention

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Country Setting Year(s)	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection
STOP-NIDDM Trial (*Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus)* Chiasson et al, 1998,[158] 2002,[136] 2003[159] *Fair*	International, multi-center, (Canada, Germany, Austria, Nordic countries, Israel, Spain) 1995 - 1998	I: 714 C: 715	3.3y (mean) 1.15y (SD)	Ages 40-70y; BMI 25-40 kg/m^2; IGT according to WHO; ≥140 and <198 mg/dl (≥7.8 and <11.1 mmol/l) (2-hr 75 g glucose) and FPG of 101-140 mg/dl (5.6-7.7 mmol/l)	CV event in the last 6m; specific/abnormal levels of serum creatinine, fasting serum TG, liver enzymes, or thyroid stimulating hormone; treated in the last 3m with glucocorticoids, beta-blockers, thiazide diuretics, or nicotine acid; taking drugs that would interfere with gastrointestinal mobility or absorption	Volunteer, 1st degree relatives of DM2 patients
Swinburn et al, 2001[157] *Fair-poor*	New Zealand 41 work sites 1988 - 1990	I: 66 C: 70 (completed y intervention) Original survey sample 4,833; study group approached 2y post original survey	5y	"Glucose intolerant group" who could be contacted 2y after original study: 2-h glucose 126-198 mg/dl (7.0 -11.0 mmol/l); Ages ≥ 40y	NR	Participants in workforce survey with "glucose intolerance" (4.8% of original survey)
Watanabe et al, 2003[155] *Fair*	Japan, Tokyo Health Clinic 2000 - 2001	I: 86 C: 87	1y	High risk for DM2: [FPG >110 and <126 mg/dl (>6.1 and <7.0 mmol/l); 2-h PG >140, <200 mg/dl (>7.8, < 11.1 mmol/l); 1-h plasma glucose ≥180 mg/dl (≥10 mmol/l)], male, aged 35-70y, living in metropolitan Tokyo	Normal FPG DM2; hypoglycemic, cholesterol lowering or antihypertensive drugs; refused to participate on questionnaire	Annual health check-up in health examination center or workplace

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Population	Existing vascular disease	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood Pressure (mm Hg)
STOP-NIDDM Trial (*Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus)* Chiasson et al, 1998,[158] 2002,[136] 2003[159] *Fair*	Race (%): Caucasian: I: 97; C: 98 Country (%): Canada: 40; Germany/Austria 27; Nordic 24; Spain 5; Israel: 5 Age y (SD): I: 54.3 (7.9); C: 54.6 (7.9) % male: I: 48; C: 50	History of CVD %: I: 5; C: 4.7 CV meds (%): I: 21.4; C: 20.1	FPG (pmol/l) (SD) I: 99.34 (57.64) C:98.13 (56.78) 2h FG (SD): I: 606.37 (437.46) C: 597.99 (414.38) A1c: NR	TC (SD): I: 196 [5.76 mmol/l (1.04)]; C: 217 [5.61 mmol/l (0.99) HDL (SD): I: 46 [1.19 mmol/l (0.32)]; C: 45 [1.17 mmol/l (0.33)] LDL (SD): I: 142 [3.66 mmol/l (0.91)]; C: 137 [3.54 mmol/l (0.90)] TG (SD): I: 183 [2.07 mmol/l (1.10)]; C: 183 [2.07 mmol/l (1.17) Overall: 58% dyslipidemia	DBP (SD): I: 82.8 (9.4) C: 82 (9.3) SBP (SD): I: 131.4 (16.3) C: 130.9 (16.2) HTN: (%): I: 52; C: 50
Swinburn et al, 2001[157] *Fair-poor*	Race: I: 67% European, 20% Pacific Islander, 10% Maori, 3% other C: 76% European, 13% Pacific Islander, 8% Maori, 4% other Age y (SEM): I: 52.5 (.8); C: 52 (.8) % male: I: 67; C: 80	NR	FPG I (SEM): 121 (SEM) [6.7 mmol/l (0.2)] C (SEM): 119 (SEM) [6.6 mmol/l (0.2)] A1c (%): NR	NR	NR
Watanabe et al, 2003[155] *Fair*	Race: NR Age y (SD): I: 52.2 (7.4); C: 54.9 (6.7) % male: NR	NR	FPG (SD): I: 110 [6.1 mmol/l (0.55)] C: 99 [5.5 mmol/l (0.55)] A1c (%): NR	TC (SD): I: 201.3 (32); C: 199.5 (37) HDL (SD): I: 52.2 (12.2); C: 52.8 (15.2) TG (SD): I: 128.6 (64); C: 127.1 (71.1) % on lipid meds: NR	DBP (SD): I: 77.4 (10.2); C: 76.4 (10.8) SBP (SD): I: 122.3 (14.4); C: 121.1 (14.3) % on anti-HTN meds: NR

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Other CVD risk factors**	**Intervention**	**Primary endpoint(s)**
STOP-NIDDM Trial (*Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus)* Chiasson et al, 1998,[158] 2002,[136] 2003[159] *Fair*	BMI: (kg/m2) (SD): I: 31 (4.3); C: 30.9 (4.2) Weight (kg) (SD): I: 87.6 (15.3); C: 87.1 (14.1) Waist circumference (SD): I: 102.1 (11.7); C: 102.2 (11.2) Smoking (%): I: 12; C: 14	All participants seen every 2m; at start received weight reduction/weight maintenance/exercise advice; dietician counseling before randomization and once every y; food and exercise, 3d diary review at each visit I: Acarbose, start at 50 mg qd, up to 100 mg tid C: Placebo tid	Progression to DM2, development of major CV events and hypertension
Swinburn et al, 2001[157] *Fair-poor*	BMI (kg/m^2) (SD): I: 29.08 (0.55); C: 29.17 (0.48) Weight (kg) (SD): I: 85.46 (1.80); C: 84.33 (1.55) Waist circumference (cm) (SD): I: 100.48 (1.42); C: 101.60 (1.28)	I: RF structured diet program; monthly small group meeting focused on education, goal-setting & self-monitoring C: CD usual; general dietary advice about health choices only at study entry	Weight, exercise, diabetes, IGT and IFG (WHO criteria)
Watanabe et al, 2003[155] *Fair*	BMI (kg/m^2) (SD): I: 24.5 (3.0); C: 21.2 (2.7) Smokers: I: 28%; C: 39%	I: NDE program: individual dietary counseling 1m post exam plus mailings at 6m, focus to decrease energy intake at night, increase fish, whole grains, vegetables C: CDE program: general oral and written results of their health exam; leaflet with prevention of lifestyle related diseases	% change 2-h PG

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Outcomes	Adherence Withdrawals (%)
STOP-NIDDM Trial (*Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus)* Chiasson et al, 1998,[158] 2002,[136] 2003[159] *Fair*	Progression to DM2: I: 221/682 (32%); C: 285/686 (42%): hazard ratio 0.75 (95% CI 0.63-0.90; between group value = 0.0015) Drug benefit regardless of age, sex, or BMI Incidence of DM2/person y: I: 101/1000; C: 121/1000 [risk difference of 9.1% over 3.3y] (no p value given) Any CV Event: I: 15/682; C: 32/686 (between-group p value = 0.02); hazard ratio: 0.51(0.28 - 0.95) acarbose had RRR of 49% and absolute RR of 2.5%; control rate of CV events 1.4%/y MI: I: 1/682; C: 12/686; Hazard ratio: 0.09 (0.01-0.72) (between-group p value=0.02) HTN: Hazard ratio 0.66 (0.48-0.89) Angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular event or stroke, or peripheral vascular disease: NSD NNT to prevent 1 CV events: 40 with IGT over 3.3y	Withdrew early: I: 211/682; 130/686 Withdrew due to AEs (%): I: 19; C: 5 Gastrointestinal AEs (mild/ moderate) (%): I: 13; C: 3* flatulence: I: 9; C: 1 diarrhea: I: 5; C: 1 abdominal pain: I: 3; C: 1 Death (%): I: 1; C: <1 Loss to follow-up (number) (%): I: 18 (3); C: 17 (2%) * (between group value=0.0001)
Swinburn et al, 2001[157] *Fair-poor*	A smaller proportion of participants had DM2 in the RF group compared to the CD group at 1y (47% compared to 67%) (p-value NR) Incidence DM2 or IGT at 1y among all participants (DM2, IGT, normal): I < C (p=0.015) NSD in incidence among groups at 2, 3, or 5y Data are for entire population, of which only 31% had IFG or IGT	136 (77%) completed 1y intervention; 104 at 2y (76% of 136); 99 at 3y (73%); 103 at 5y (76%) Compliance assessed by attendance at monthly meetings and completion of diet diaries 40 participants did not complete the study: 4 died, 1 became pregnant, 7 developed serious illnesses, 4 moved, 24 dropped out
Watanabe et al, 2003[155] *Fair*	Incidence in diabetes between the two groups was not significant (data NR)	156 (90.2%) completed y 1 17 subjects left the study: 1 changed jobs, 5 retired (I: 1; C: 4); 1 for financial reasons C; 10 could not be located (I: 6; C: 4)

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Adverse Events**	**Other Results**
STOP-NIDDM Trial (*Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus)* Chiasson et al, 1998,[158] 2002,[136] 2003[159] *Fair*	Overall: I: 98; C: 95 Gastrointestinal: I: 83; C: 60 Flatulence: I: 68; C: 27 Diarrhea: I: 32; C: 17 Abdominal pain: I: 17; C: 12 Dyspepsia: I: 7; C: 9 Nausea: I: 5; C: 5 Constipation: I: 4; C: 5 Gastroenteritis: I: 4; C: 5 General symptoms: I:58; C: 62 Cardiovascular: I: I: 31; C: 40 Respiratory: I: 32; C: 39 Musculoskeletal: I: 34; I: 39 Metabolic and Nutritional: I: 31: C: 32 Nervous: I: 27; C: 31 Urogenital: I: 25; C: 28 Skin: I: 21; C: 24 Haematological / lymphatic: I: 4; C: 6 Endocrine: I: 4; C: 4 No serious events related to the study drug	
Swinburn et al, 2001[157] *Fair-poor*	NR	Intervention showed a significant effect on OGTT (p= 0.015) at 1y No intervention effect at 2, 3, or 5y No overall effect of diet on FBG, a significant effect on 2-h glucose over the period (p<0.0001) Compliers showed a significantly lower FBG (p=0.041) and 2-h BG 5 y (p= 0.023) Data are for entire population (IGT, IFG, normal)
Watanabe et al, 2003[155] *Fair*	NR	% changes in FPG or 1-h PG between groups; 2-h PG was significantly different (P <0.001) [I: -8.2 (1.9); C: 11.2 (3.0)]; Of note: FPG and 2-h PG were significantly different between groups at baseline (P<0.05 and P<0.01, respectively)

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Country Setting Year(s)	Treatment groups Sample size	Length of follow-up	Inclusion criteria	Exclusion criteria	Participant selection
XENDOS Study (*XENical in the prevention of Diabetes in Obese Subjects)* Torgerson et al, 2004,[161] 2001[160] *Fair-poor*	Sweden 22 Medical Centers 1997 - 2002	I: Lifestyle/orlistat 1,650 [350 IGT] C: Lifestyle only 1,655 [344 IGT] ITT population: I: Lifestyle/orlistat 1,640 C: Lifestyle only 1,637	4y	30-60y NGT: 2-h 75 g OGTT whole blood glucose <180 mg/dl (<10.0 mmol/l) and fasting whole blood glucose 121mg/dl (<6.7 mmol/l); or IGT: fasting whole blood glucose <121 mg/dl (<6.7 mmol/l) and 2-h whole blood glucose 121-180 mg/dl (6.7-10.0 mmol/l]; BMI $\geq$30kg/m^2	DM2, myocardial infarction in last 6m, change in body weight >2 kg from screening to baseline measurements, SBP > 165 mm Hg or DBP > 105 mm Hg on 2 visits, cholelithiasis, gastrointestinal surgery for weight reduction, peptic ulcer, gastrointestinal disease, pancreatic disease, malignancy, psychiatric or neurologic disorder, abuse or previous participation in any trial of orlistat	Advertisement, volunteers, 22 medical centers

Abbreviations: ACE-I, angiotension converting enzyme inhibitor; AE, adverse event; ARR, absolute risk reduction; BG, blood glucose; bid, two times daily; BMI, body mass index; BP, blood pressure; C, control group; CD, Controlled Diet; CDE, conventional dietary education; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; d, day; DBP, diabolic blood pressure; DM, diabetes; DM2, type 2 diabetes; DPP, Diabetes Prevention Program; FBG, fasting blood glucose; FG, fasting glucose; FPG, fasting plasma glucose; GI, gastrointestional; h, hour; HDL, high density lipoprotien cholesterol; HR, hazard ratio; HTN, hypertension; I, intervention group; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ITT, intention to treat analysis; LDL, low density lipoprotein cholesterol; LSM, lifestyle modification; LTPA, leisure time physical activity; m, months; MI, myocardial infarction; meds, medicines; min, minutes; NDE, new dietary education; NGT, normal glucose tolerance; NHANES, National Health and Nutrition Examination Survey; NNT, number needed to treat; NR, not reported; NSD, no significant difference; OGTT, oral glucose tolerance test; PA, physical activity; PG, plasma glucose; PP, postprandial plasma; PPG, postprandial plasma glucose; q, every ; QOL, quality of life; RF, reduced fat; RRR, relative risk reduction; SBP, systolic blood pressure; SD, standard deviation; SEM, standard error of the mean; TC, total cholesterol; TG, triglycerides; tid, three times daily; US, United States; w, week; WHO, World Health Organization; y, year.

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Population	Existing vascular disease	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood Pressure (mm Hg)
XENDOS Study (*XENical in the prevention of Diabetes in Obese Subjects)* Torgerson et al, 2004,[161] 2001[160] *Fair-poor*	Race: NR Age y (SD): I: 43 (8); C: 43.7 (8) % male: I: 44.8; C: 44.7	None existing	FBG (SD): I: 83 [4.6 mmol/l (0.6)] C: 81 [4.5 mmol/l (0.6)] A1c (%): NR	TC (SD): I: 224 [5.8 mmol/l (1.0)]; C: 224 [5.8 mmol/l (1.0)] LDL (SD): I: 143 [3.7 mmol/l (0.9)]; C: 147 [3.8 mmol/l (0.9)] HDL (SD): I: 46 [1.2mmol/l (0.3)]; C: 46 [1.2 mmol/l (0.3)] TG (SD): I: 168 [1.9 mmol/l (1.0)]; C: 168 [1.9 mmol/l (1.2)] % on lipid meds: NR	DBP (SD): I: 82 (10); C: 82.3 (10) SBP (SD): I: 130.8 (15.8); C:130.4 (15.4) % on anti-HTN meds: NR

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Other CVD risk factors**	**Intervention**	**Primary endpoint(s)**
XENDOS Study (*XENical in the prevention of Diabetes in Obese Subjects)* Torgerson et al, 2004,[161] 2001[160] *Fair-poor*	BMI (kg/m^2) (SD): I: 37.3 (4.2); C: 37.4 (4.5) Weight (kg) (SD): I: 110.4 (16.3); C: 110.6 (16.5) Waist circumference (cm) (SD): I: 115.0 (10.4); C: 115.4 (10.4)	All subjects: Dietary counseling every 2w 1st 6m, then monthly; exercise encouragement [Diet: ~800 kcal/d deficit, 30% of calories from fat, ≤300 mg cholesterol/d] C: Placebo tid I: Orlistat 120 mg tid	Primary: time to onset of DM2; change in body weight Secondary: anthropometric measurements, metabolic profile, time to onset of IGT

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name Author, year *Quality Rating*	Outcomes	Adherence Withdrawals (%)
XENDOS Study (*XENical in the prevention of Diabetes in Obese Subjects)* Torgerson et al, 2004,[161] 2001[160] *Fair-poor*	Main analysis: I group showed significantly decreased progression to DM2 compared with C plus lifestyle change (between group p-value = 0.0032); Cumulative incidence rates after 4y: I:6.2% vs. C: 9.0% Hazard ratio (0.627 [95% CI 0.455-0.863]); risk of DM2 with I vs C Sub-analysis: In patients with IGT at baseline: I showed significant decreased progression to DM2 when diagnosed on the basis of a single test (between group p-value = 0.0024) and by repeat positive testing (between group p-value =0.0171); those with IGT were more likely to develop DM2 over 4y than those with NGT (hazard ratio 10.60 [95% CI 7.30-15.40] p<0.0001)	Adherence: ITT population: diet and exercise similar in both groups over 4y period Study drug administration: I: 93.3%; C: 92.8%, NSD. Withdrawals: I: 52%; C: 34% completed the study, between group p-value < 0.0001 Reasons: Refusal of treatment (I: 14%, C: 20%); insufficient therapeutic response (I: 8%, C: 19%)

APPENDIX B9. RANDOMIZED CONTROLLED TRIALS OF PREDIABETES (KQ3)

Study name **Author, year** ***Quality Rating***	**Adverse Events**	**Other Results**
XENDOS Study (*XENical in the prevention of Diabetes in Obese Subjects)* Torgerson et al, 2004,[161] 2001[160] *Fair-poor*	No deaths were attributed to study medication 4% C vs. 8% I withdrew due to AEs or laboratory abnormalities (mostly gastrointestinal events) More mild to moderate gastrointestinal events in 1st y with I compared to C group (91% vs. 65% in YR 1; 36 vs. 23% in YR 4) At least one serious AE (I:15%; C: 13%); 2% serious gastrointestinal events in I and C	

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Objective	Type of screening or perspective	Type of model	Population; Country	Included costs	Discount rate
Segal et al, 1998[173]	To determine the CE of a lifestyle intervention for DM2 prevention relative to other health programs	Health care system	Markov	Based on Australian cohort; cohorts with IGT, normoglycemia and DM2 Australia	Program costs and direct medical costs	5%/y for benefits and costs
Caro et al, 2004[174]	To compare the health and economic outcomes of using acarbose and an intensive lifestyle program to prevent progression to DM2 of persons with IGT	Health care system	Monte Carlo simulation to evaluate a Markov process	Representative cohort of 1000 Canadians with IGT 2-h glucose 7.8-11.1 mmol/l Canada	Direct medical costs	5%/y cost and health outcomes
Palmer et al, 2004[176]	To establish whether DPP interventions are cost effective in various countries	Health care system	Markov	Resembled the DPP population (IGT 5.3 -7.0 mml/l): mean age 50.6y, BMI 34.0 32% from minority population Various countries	Direct medical costs	5%/y for costs and outcomes

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Base case assumptions	Time horizon	Data sources	Sensitivity analyses	Intervention
Segal et al, 1998[173]	Reduction in LE for DM2 is 2-3y and 0.5-3y for excess weight compared to normoglycemic and BMI<25; cost of DM2/y is $1800 Australian $; only benefits of program relate to effects on incidence of DM2 and life years; QOL ignored (insufficient data); lifestyle reduced incidence DM2 from 70% to 30% in obese; progression among stages at 5y intervals	25y	Various trial and observational data with follow-up >5y	Varied % successful at weight loss, discount rate, program cost, effect on incidence, life expectancy	1. Intensive weight loss and fitness program for obese 2. Standard care
Caro et al, 2004[174]	Treatment for 5y; prevalence IGT 11%; reduction in rate of transition to DM2: metfomin 21%, acarbose 36%, lifestyle 58%; annual probability of transitioning to DM2 6.3%	10y or death	Various epidemiological data sources; STOP-NIDDM; DPP, Diabetes Prevention Study; Ontario cost data	Change risk of transition to DM2; intervention effectiveness; costs	1. Acarbose 2. Metformin 3. Intensive lifestyle 4. No treatment
Palmer et al, 2004[176]	Time from onset to diagnosis of DM2 8y; RR for all-cause mortality 1.76 for diagnosis DM2 and 2.26 for diagnosed DM2; side effects from metformin based on DPP data; duration of effects do not persist beyond 3y trial period	Lifetime	DPP, UKPDS	Age, BMI groups, costs, transition probabilities; costs, discount rate	1. Intensive lifestyle (DPP intervention) 2. Metformin 3. Control

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Outcomes	Conclusions	Quality assessment
Segal et al, 1998[173]	Net cost per life-year saved for persons with IGT (US$): Behavioral program for seriously obese: net saving Surgery for BMI >40: $3300	Primary prevention of DM2 for persons with IGT is relatively cost-effective	Did not model individual complications Used only one set of transition probabilities; overly simplistic; based on older epidemiologic data and small trials Assumptions not transparent
Caro et al, 2004[174]	Incremental cost per life-year gained: relative to no treatment: Metformin: Cost savings Acarbose: Cost savings Lifestyle: $749	Treatment of IGT to prevent DM2 is cost-effective: lifestyle interventions lead to greatest healthy benefits at reasonable cost	Did not incorporate QOL Assumptions not transparent
Palmer et al, 2004[176]	Mean number of years free from diabetes: Lifestyle: 10.0 Metformin: 9.0 Control: 8.1 Incremental increase in LE if treatment effect lasted a lifetime in years, vs control: Lifestyle: 0.90 Metformin: 0.35 Lifestyle and metformin cost savings in most countries Metformin had more impact on decreasing costs in increasing life expectancy in younger & more obese patients	DPP produces clinically important improvements in LE, with either overall cost savings or minor increases in total costs per patient	Did not model individual complications Transparent reporting; adequate reporting of data sources and synthesis methods

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Objective	Type of screening or perspective	Type of model	Population; Country	Included costs	Discount rate
Archimedes Model Eddy et al, 2005,[169] 2003[170, 171]	To estimate the effects of the lifestyle modification program used in the DPP on health and economic outcomes	Patient, health plan, societal	Cost-effectiveness analysis using Archimedes model (built from underlying anatomy, biological variables, and pathways)	Adults at high risk for DM2 (BMI >24 kg/m2, FPG 95-125 mg/dl, or 2-h OGTT 140-199 mg/dl); 100,000 simulated persons for health plan United States	Direct and indirect (for societal perspective)	3% annual rate
CDC/RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* Herman et al, 2005[172]	To estimate the cost-utility of the DPP interventions compared to the placebo intervention	Opportunistic screening Health care system and societal	Markov; modified CDC/RTI model using costs and data from DPP, quality of life associated with IGT, and UKPDS data on diabetes progression and complications	DPP population: 3234 nondiabetic persons ≥ 25y with IGT and FPG 95-125 mg/dl; mean age 51y, 68% female; 45% members of racial/ethnic minority groups United States	Health care system perspective: direct medical costs; societal perspective: also included direct nonmedical costs	3% annual rate for costs and QALYs; clinical outcomes not discounted Costs in 2000 US$
Lindgren et al, 2007[177]	To assess the cost-effectiveness of the Finnish Diabetes Prevention Study	Health care system	Markov state transition model with seven states using yearly cycles; model evaluated using Monte Carlo simulation	Population-based screening in Stockholm; 60y old men and women Sweden	Direct and indirect medical costs	3% annual rate for costs and benefits

Abbreviations: bid, twice daily; BMI, body mass index; CE, cost effectiveness; CHD, coronary heart disease; DM2, type 2 diabetes; DPP, Diabetes Prevention Program; ESRD, end stage renal disease; FPG, fasting plasma glucose; HTN, hypertension; IGT, impaired glucose tolerance; LE, life expectancy; MI, myocardial infarction; min, minutes; NNT, number needed to treat; nonDM, without diabetes; OGTT, oral glucose tolerance test; preDM, prediabetes; QALY, quality-adjusted life year; QOL, quality of life; RR, relative risk; STOP-NIDDM, Study TO Prevent Non Insulin Dependent Diabetes Mellitus; UKPDS, United Kingdom Prospective Diabetes Study; US, United States; y, year.

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Base case assumptions	Time horizon	Data sources	Sensitivity analyses	Intervention
Archimedes Model Eddy et al, 2005,[169] 2003[170, 171]	Health plan 10% turn over per y; effectiveness and costs observed at end of the DPP persist as long as the person was receiving the lifestyle intervention; weight increased to 4% loss after 3y and persisted	5 to 30y (for societal)	Data derived from variety of empirical sources; no data are assumed; costs from DPP study, Kaiser Permanente, and others	Model compared to clinical trials to validate; cost of lifestyle intervention was varied and is cost-saving over 30y if it cost $100/y	1. DPP lifestyle program 2. Baseline: no lifestyle or other intervention 3. Lifestyle when FPG>125 mg/dl 4. Metformin as in DPP study
CDC/RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* Herman et al, 2005[172]	Placebo intervention: annual hazard of DM2 was 10.8/100 person-years. At 3y follow-up the RR for lifestyle and metformin interventions were 55.8% and 29.9%; assume these interventions were applied until diabetes onset and that the health and quality of life benefits associated with the interventions persisted until diabetes onset; baseline rates of complications: neuropathy 8.5%, HTN 28%, dyslipidemia 45%, smokers 7%, history of MI 2.0%; nonDM-related mortality for persons with IGT was the same as for persons with DM2; 10y delay between onset and clinical diagnosis of DM2; microvascular complications did not progress during prediabetes; macrovascular risk factors and disease progress during prediabetes	Lifetime	DPP, UKPDS	Age groups, group vs individual program, metformin cost, varying adherence rates, reduced costs and effectiveness; discount rates delay from onset to diagnosis of DM2 Results: Lifestyle is CE in all age groups; metformin not CE in >65y	DPP lifestyle intervention: 7% or more weight loss and 150 min/week of activity; or metformin 850mg bid; or placebo
Lindgren et al, 2007[177]	Risk of developing DM2 6%/y; risk of MI based on UKPDS; lifestyle intervention produces relative risk of DM2 of 0.4; no lasting effect of intervention after treatment was discontinued	6y (longest follow-up of Finnish Study	Finnish Diabetes Study, UKPDS, Swedish cost data	Discount rate; including costs in added years of life; various cost estimates	Lifestyle intervention

APPENDIX B10. STUDIES MODELING TREATMENT OF PREDIABETES (KQ3)

Model Author, year (in date order)	Outcomes	Conclusions	Quality assessment
Archimedes Model Eddy et al, 2005,[169] 2003[170, 171]	Individual at high-risk, 30y probability of developing DM2: baseline 72%; lifestyle: 61%, NNT for benefit: 9; metformin 68% Societal perspective: Incremental 30-y cost/QALY: DPP lifestyle for all compared to lifestyle when FPG >125mg/dl: $201,818; Lifestyle when FPG>125 mg/dl compared to baseline: $24,523; compared to baseline, lifestyle intervention for all high-risk would be $62,600/QALY Health plan perspective: 30y cost/QALY of DPP lifestyle program compared to no intervention $143,000; increases with decreased time horizon and smaller plans; over 5y: $2.7 million	Compared to no prevention program, the DPP lifestyle program reduces preDM person's 30y risk of DM2 from 72% to 61%; 30-y cost/QALY of the DPP lifestyle intervention compared to doing nothing from health plan perspective: $143,000; societal perspective: $62,000 Delaying the lifestyle intervention until after diagnosis of DM2 or using metformin: cost/QALY gained compared to no program: $24,500 and $35,400 Marginal cost-effectiveness of DPP lifestyle program for preDM compared to waiting until after DM2 diagnosed: cost/QALY: $201,800	Validated model Extensive sensitivity analyses Some assumptions not transparent Considers multiple disease processes and transitions
CDC/RTI Model (*Centers for Disease Control and Prevention / Research Triangle Institute)* Herman et al, 2005[172]	Delay in onset DM2: compared to placebo intervention, lifestyle delays onset by 11y and metformin by 3y Lifetime development of DM2: 83% in placebo, 63% with lifestyle, 75% with metformin Increase in LE compared to placebo: lifestyle 0.5y, metformin 0.2y Reduction in cumulative incidence complications: Lifestyle vs placebo: blindness 39%, ESRD 38%, amputation 35%, stroke 9%, CHD 8% Metformin vs placebo: blindness 16%, ESRD 17%, amputation 16%, stroke 3%, CHD 2% Incremental cost/QALY compared to placebo: Lifestyle: $1,124; metformin: $31,286 lifestyle intervention cost saving in <45y old	Lifestyle interventions are relatively CE compared to placebo, producing gains in survival and a decrease in microvascular and cardiovascular complications	Extensive sensitivity analyses Transparent reporting, adequate reporting of data sources and synthesis methods
Lindgren et al, 2007[177]	Intervention is associated with an increase in survival of 0.18y; mean QALYs gained: 0.20y; the cost-effectiveness ratio is Euros 2,363/QALY	This model predicts that the Finnish Diabetes Study lifestyle intervention targeted at persons with high risk would be cost-savings for the health case plan and cost-effective for society	Not assessed

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design	Purpose of study	Country; Setting; Year(s) of study	Treatment groups; Sample size	Length of follow-up	Inclusion criteria
ADDITION Study Thoolen et al, 2006[188] *Not rated*	2X2 factorial (based on time since diagnosis and treatment intensity) cross-sectional study	Investigate how time since diagnosis and treatment intensity influences psychological outcomes in patients with screen-detected DM2	Southwest Netherlands Multi-center (79 general practices)	468 invited 227 agreed 206 completed questionnaire 196 included in analysis (10 not included because time since diagnosis occurred between 1-2y, so did not fit parameters)	No follow-up	Patients included in Dutch arm of ADDITION study without serious comorbidities Ages 50-69 Diagnosed with DM2 3-33m previously Receiving usual or intensive treatment From ADDITION STUDY: Screening study: Without known DM2 Identified though specific centers Treatment study: Newly diagnosed DM2, defined by 99 mg/dl (5.5 mmol/l), by fasting and 2-h post-glucose-challenge blood glucose measurements
ADDITION Study Eborall et al, 2007[190] *Fair*	Controlled clinical trial (embedded within the ADDITION Trial)	To quantify the psychological impact of primary care-based stepwise screening for DM2	United Kingdom (Cambridge)	Screened: 4370 Control: 964	Up at 15m	From ADDITION screening study: Without known DM2 Identified though specific clinical centers
ADDITION Study Eborall et al, 2007[189] *Not rated*	Prospective qualitative interview of patients in a screening program for DM2	To provide insight into factors that contribute to the anxiety reported in the quantitative study of the psychological effect of screening for DM2; to explore expectations and reactions to the screening experience	United Kingdom (Cambridge)	23 total	No follow-up	From ADDITION screening study: Without known DM2 Identified though specific clinical centers

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Exclusion criteria	Participant selection	Population	SES or educational level	Pre-existing depression, anxiety analyzed, etc	Existing vascular disease
ADDITION Study Thoolen et al, 2006[188] *Not rated*	From ADDITION STUDY: Screening study: Previously diagnosed DM2 Treated with blood glucose lowering agents Treatment study: IGT and IFG, contraindications or intolerance to study medications, alcoholism, drug abuse, psychosis or emotional problems, malignant disease with a poor prognosis, pregnant or lactating	Screen-detected	Mean age: 61-62y (~5y SD) % male ("marginal difference" between groups, ns): Group 1: 71 Group 2: 50 Group 3: 63 Group 4: 57	Educational level*: Group 1: 3.0±1.6 Group 2: 3.0±1.4 Group 3: 3.4±1.6 Group 4: 3.0±1.7 *Measured on a 6 point scale (1=primary to 6=higher education)	NR	NR
ADDITION Study Eborall et al, 2007[190] *Fair*	See above	Recruitment from clinical settings	65% male Mean age: 58y Avg BMI: 30.5 NSD between groups	NR for these specific groups (see above)	NR	NR
ADDITION Study Eborall et al, 2007[189] *Not rated*	See above	Recruitment from clinical settings	Population scheduled for OGTT was sampled; additional sampling to address imbalance of sex and diagnosis with initial sampling	NR	NR	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood pressure (mm Hg)	Other risk factors (CVD, etc)	Measures used
ADDITION Study Thoolen et al, 2006[188] *Not rated*	NR	NR	NR	BMI (from self-report) mean (SD): Group 1: 29.0 (4.3) Group 2: 29.4 (4.7) Group 3: 30.0 (4.9) Group 4: 30.0 (4.9)	Hospital Anxiety and Depression Scale (HADS): measure emotional outcomes, including anxiety and depression [standardized] Problem Areas in Diabetes (PAID) Scale: measure diabetes distress [standardized] Cognitive variables included: 1) perceptions of health threat - measured by a) perceived seriousness of [based on Diabetes Illness Representations Questionnaire], and b) vulnerability for diabetes [not standardized] 2) self-efficacy - measured by combination of a) Lorig 1996, and b) Kuijer and de Ridder 2003 scales [not standardized] Self-care behavior measured using revised summary of diabetes self-care activities measure [parts valid]
ADDITION Study Eborall et al, 2007[190] *Fair*	NR	NR	NR	BMI >30kg/m^2: (mean [SD]) I: 30.5 (4.7) C:30.6 (4.9)	Spielberger state anxiety inventory, range from 20-80 Hospital Anxiety and Depression Scale (HADS): measure emotional outcomes, including anxiety and depression [standardized] Single item on general health Disease-specific worry: adapted from legman cancer worry scale: sum scores 6-24
ADDITION Study Eborall et al, 2007[189] *Not rated*	NR	NR	NR	NR	Open-ended questions

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Intervention	Primary endpoint(s)	Outcomes for standardized measures	Adherence withdrawals (%)
ADDITION Study Thoolen et al, 2006[188] *Not rated*	4 groups created by categories of usual or intensive multifactorial drug treatment and time since diagnosis (<1 y or 2-3 y) Multivariate analysis used to examine variation in outcomes on time since diagnosis and treatment intensity <u>4 groups analyzed</u>: Group 1: DM <1y time since diagnosis + usual care Group 2: DM <1y time since diagnosis + intensive treatment Group 3: DM 2-3y time since diagnosis + usual care Group 4: DM 2-3y time since diagnosis + intensive treatment	7 variables: Anxiety, depression, diabetes-related distress, perceived seriousness and vulnerability, self efficacy, and self-care	"Most patients reported little distress, low perceived seriousness and vulnerability, high self-efficacy, and low self-care, but outcomes varied considerably across conditions" Time effects found for perceived vulnerability (increases significantly with time since diagnosis) (F=14.3, p<0.001) No time effects found for anxiety (F=0.3, ns) nor depression (F=1.2, ns) No time effects found for diabetes distress (F=3.0, ns), perceived seriousness (F=1.8, ns), self efficacy (F=0.2, ns), nor self management (F=0.0, ns) Some reported clinically relevant anxiety (HADS score >8; clinically definite scores >11) in group diagnosed < 1 year, but it seems to be effect of intensive treatment x time, because the intensive treatment group is significantly higher (mean scores, 6.8 vs 4.5, F=5.8, p<0.001). 2-3y group mean scores = 5.0 vs 5.5, ns	NR
ADDITION Study Eborall et al, 2007[190] *Fair*	Step-wise screening for DM2: hi-risk for DM2 were identified using computerized general practice records; those were invited to get random BG; if >5.5 mmol/l invited for fasting BG, if >6.1 mmol/l invited for 75-g OGTT	State anxiety, anxiety, depression, diabetes-specific worry, self-rated health	Conclusion: screening has limited psychological impact on patients; being required to return for further tests after an initial positive random BG has small negative psychological impact of doubtful clinical significance Immediate impact of initial (+) screening test compared to test (-): poorer health; higher anxiety, depression, diabetes-specific worry (p all ≤ 0.05)	Invited to screening and did not attend; 32% Random BG (-) at baseline: 67% follow-up at 12-15m Random BG (+) at baseline: 39% follow-up at 12-15m
ADDITION Study Eborall et al, 2007[189] *Not rated*	As above	Perceptions and expectations before and after OGTT	Initial stages of screening processes: most participants not very worried who tested (+) on the first tests Prediagnostic test expectations: many accepted possibility of (+) diagnosis Reactions after new diagnosis of DM2: tendency to downplay importance; all had plans to control the disease; most were grateful for screening program Diagnosed with IFG or IGT: many were confused by this diagnosis; most were unconcerned and unaware of this diagnosis as a risk factor for DM2 or CVD	None

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Other results	Comments	Funding
ADDITION Study Thoolen et al, 2006[188] *Not rated*	Related to treatment: Time x treatment interactions found for anxiety (F=5.8, p<0.01), diabetes-related distress (F=4.6, p<0.05), and self-efficacy (intensively treated patients showed more distress and less self-efficacy in 1st y; usual care patients reported more distress and less self-efficacy 2-3y after diagnosis (F=7.1, p<0.01)	Included participants were more educated and reported lower self-management than non-participants Analysis adjusted for sex, BMI, and number of complaints Psychological effects were not associated with sociodemographic variables, but were associated with BMI and medical complaints	NR
ADDITION Study Eborall et al, 2007[190] *Fair*	Test for trend over steps in screening process: worry about DM increased as underwent more screening tests before testing (-) Nonattenders for the initial test: 11% response rate at 12-15m: had high worry at 12-15m (p=0.03)		Wellcome trust, National Health Service Research and Development
ADDITION Study Eborall et al, 2007[189] *Not rated*	None		Royal College of General Practitioners scientific foundation board for this study; ADDITION funded by Wellcome trust, National Health Service Research and Development

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design	Purpose of study	Country; Setting; Year(s) of study	Treatment groups; Sample size	Length of follow-up	Inclusion criteria
Edelman et al, 2002[182] *Good*	Cohort with comparison (nondiabetic) group	Determine effects of new diagnosis of DM2 discovered by systematic screening	United States Durham Veterans Affairs Medical Center, North Carolina (single center) October 1996 - March 1999	1253 total (1,177 without DM2 at screening; 56 [4.5%] with new diagnosis of DM2 at screening)	1y	Durham Veterans Affairs Medical Center outpatients that did not report having diabetes at start of study
Farmer et al, 2003[183] *Good-fair*	Single-group cohort	To assess changes in anxiety, well-being, and cognitions associated with screening for DM2 in people at increased risk of DM2 after 1y to identify potential predictors of increased anxiety and lower well-being	United Kingdom, Oxfordshire and South Northamptonshire 1996 - 1998	431 total	1y	Probands: Age ≥ 35 at diagnosis Families with ≥ 3 siblings, and a quarter of families with 2 siblings living within study area Participants: Participants aged 35-74 Family history of DM2 Not known to have DM2 Able to complete questionnaires
Farmer et al, 2005[184] *Fair*	Randomised controlled trial	To assess the impact on response rates and psychological measures of different follow-up schedules in at-risk participants undergoing screening for DM2	United Kingdom, Oxfordshire and South Northamptonshire	431 total Limited follow-up (LF): 213 Intensive follow-up (IF): 218	1m 6m 1y	Probands: Aged ≥ 35 at diagnosis Families with ≥ 3 siblings, and a quarter of families with 2 siblings living within study area Participants: Participants aged 35-74 Family history of DM2 Not known to have DM2 Able to complete questionnaires

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Exclusion criteria	Participant selection	Population	SES or educational level	Pre-existing depression, anxiety analyzed, etc	Existing vascular disease
Edelman et al, 2002[182] *Good*	Known diabetes Patients who had a prescription filled for hypoglycemic medication Short life expectancy (incurable cancer, heart or lung disease requiring oxygen) No easy access to a telephone	Systematically screened for DM2	Ages: 55y mean (6y SD) 94% male Race: 69% Caucasian 29% African American 2% Other	NR	Yes	NR
Farmer et al, 2003[183] *Good-fair*	Participants: Known DM2 < age 35 or > age 74	Recruited with information from general practitioners Probands sent questionnaires to assess willingness of siblings to participate	Mean age (SD) & % male: Normal risk of DM: 57.3y (10.2y) & 38.8% Borderline risk of DM: 59.8y (8.9y) & 48.5% High risk of DM: 59.8y (9.0y) & 56.5% Possible diabetes: 58.7y (9.0y) & 72.2%	Occupational group (manual/professional %): Normal risk of DM: 139/86 Borderline risk of DM: 61/38 High risk of DM: 50/31 Possible diabetes: 12/6	Yes	NR
Farmer et al, 2005[184] *Fair*	Participants: Known DM2 < age 35 or > age 74	Recruited with information from general practitioners Probands sent questionnaires to assess willingness of siblings to participate	Mean age (SD): LF: 58.8y (9.5y) IF: 58.1y (9.9y) % Male: LF: 48.8 IF: 42.7	Occupational group (manual / professional %) LF: 61.4/81 IF: 63/37	Yes	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood pressure (mm Hg)	Other risk factors (CVD, etc)	Measures used
Edelman et al, 2002[182] *Good*	NR	NR	NR	Body weight: 60% > 120% of ideal body weight Comorbidity: 95% comorbid illness; 34% moderate to severe comorbidity	Prior to study, A1c measurements taken on all subjects: A1c > 6.0% were repeated DM2 defined as A1c > 7.0% or fasting plasma glucose > 126 mg/dl (7.0 mmol/l) Health-related quality of life (HRQoL) assessed using Medical Outcomes Study Short Form 36 (SF-36). 2 parts: Physical Component Scale (PCS) and Mental Component Scale (MCS) Comorbidity assessed using Kaplan-Feinstein Index
Farmer et al, 2003[183] *Good-fair*	NR	NR	NR	Mean BMI (SD): Normal risk of DM: 27.3 (5.3) Borderline risk of DM: 28.4 (4.6) High risk of DM: 29.9 (5.3) Possible diabetes: 31.6 (5.9)	Response rates calculated Speilberger State Anxiety Inventory (SSAI-SF) Well-being questionnaire (WBQ-12) Health Anxiety Inventory (HAI)
Farmer et al, 2005[184] *Fair*	Plasma glucose: (LF then IF) Normal (<101 mg/dl [<5.6 mmol/L]: 112, 115 Borderline (101-108 mg/dl [5.6-6.0 mmol/L]) 50, 51 At risk (>108-<142 mg/dl [> 6.0-<7.9]): 43, 42 Diabetes (≥142 mg/dl [≥7.9 mmol/l]): 8, 10	NR	NR	BMI (mean): LF: 27.7 IF: 28.6	Response rates calculated Speilberger State Anxiety Inventory (SSAI-SF) Well-being questionnaire (WBQ-12)

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Intervention	Primary endpoint(s)	Outcomes for standardized measures	Adherence withdrawals (%)
Edelman et al, 2002[182] *Good*	HRQoL measured at baseline and 1y after diagnosis using multivariate analysis	HRQoL	No significant differences (p<0.05) between patients with and without DM2 nor between baseline and 1y follow-up Baseline PCS: NonDM2 vs. newly diagnosed DM2 (36.3 vs. 35.6) not different (p=0.67) Baseline MCS: NonDM2 vs. newly diagnosed DM2 (49.6 vs. 48.8) not different (p=0.70) 1y follow-up PCS: NonDM2 vs. newly diagnosed DM2 (35.2 vs. 34.6) not different (p=0.68) 1y follow-up MCS: NonDM2 vs. newly diagnosed DM2 (48.2 vs. 48.0) not different (p=0.94)	NR
Farmer et al, 2003[183] *Good-fair*	Questionnaires at baseline and 1y follow-up Analysis separated according to those receiving a "normal" test result <5.5 mmol/L compared with those "at risk" receiving a borderline (99-108 mg/dl [5.5-6.0 mmol/L]), high (>108-140 mg/dl [>6.0-7.8 mmol/L]), or test result indicating diabetes (140 mg/dl [>7.8 mmol/L])	Anxiety Well-being Cognition	Anxiety decreased from 34.5 (95% CI 33.4-35.6) to 32.3 (31.2-33.4) at 1y (p<0.0001) Well-being scores increased (improved) from 26.8 (26.0-27.4) to 27.4 (26.7-28.1)(p=0.008). Anxiety and well-being over 1y did not differ between participants receiving a normal or at-risk result	328 (76%) returned questionnaires at 1y
Farmer et al, 2005[184] *Fair*	Random assignment to either limited follow-up (1y) or intensive follow-up (1m, 6m, 1y) Analysis separated according to follow-up rates only	Response rates Anxiety Well-being	No significant difference between groups in SSAI-SF (anxiety) change scores from baseline to 1y follow-up (p=0.13) Limited follow-up group had greater improvement in well-being (change score of the WBQ-12 well-being, p= 0.003	10% failed to return SSAI-SF follow-up 11.2% failed to return WBQ-12 follow-up

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Other results	Comments	Funding
Edelman et al, 2002[182] *Good*	Mild-severe comorbid illness associated with lower PCS both at baseline and 1y follow-up (p<0.05)		Supported by Department of Veteran's Affairs Cooperative Studies and a Research Career Award
Farmer et al, 2003[183] *Good-fair*	None	BMI and gender (more female) significantly different between groups, p <0.001 and p=0.002 respectively. Same population as Farmer, 2005	Scientific Foundation Board of the Royal College of General Practitioners, funded by National Health Service Career Development Award
Farmer et al, 2005[184] *Fair*	No difference between groups in proportion of 1y response questionnaires returned	If group slightly more likely to be female, heavier, higher baseline WBQ-12 score Focused on differences between 1 vs. 3 follow-up questionnaires, *so groups not very meaningful for our purposes* Same population as Farmer, 2003	Scientific Foundation Board of the Royal College of General Practitioners, funded by National Health Service Career Development Award

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design	Purpose of study	Country; Setting; Year(s) of study	Treatment groups; Sample size	Length of follow-up	Inclusion criteria
Hoorn Study Adriaanse et al, 2002[181] *Not rated*	Cohort study with comparison (nondiabetic) group (pilot study)	To explore psychological impact of a stepwise population-screening project for DM2	Netherlands, Hoorn region	40 total (11,679) Diagnosed with DM2: 20 At increased risk: 20	Screen-diagnosed diabetes group: 2m Elevated risk group (controls): 2w	Participant in Hoorn screening project and chosen to be part of pilot study DM2 or elevated risk of DM2 (SRQ score > 6) Ages 51-74
Hoorn Study Adriaanse et al, 2004[178] *Fair*	Cohort study with comparison group (both with DM2)	To determine prospectively health-related quality of life during 1st y following diagnosis of DM2, in newly diagnosed patients in general practice, compared with patients detected early by targeted population screening	Netherlands, Hoorn region	165 total GPDM (general practice diagnosed diabetes): 49 SDM (screening diagnosed diabetes): 116	2w 6m 1y	SDM: Participant in Hoorn screening project and chosen to be part of this study, with DM2, ages 50-75 GPDM: cities of Den Helder and Medemblik, 36 general practices, 1999-2001, with DM2, ages 50-75
Hoorn Study Adriaanse et al, 2004[180] *Fair*	Cohort with comparison (nondiabetic) group	To examine impact of diagnosis of DM2 on psychological well-being and perceived health status in subjects who participated in a targeted population-screening program	Netherlands, Hoorn region	259 total (from 11,679) Subsequently diagnosed with DM2: 116 Without DM2 143	2w 6m 1y	Participant in Hoorn screening project and chosen to be part of this study, with DM2 or elevated risk of DM2 (SRQ score > 6) Ages 51-74

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Exclusion criteria	Participant selection	Population	SES or educational level	Pre-existing depression, anxiety analyzed, etc	Existing vascular disease
Hoorn Study Adriaanse et al, 2002[181] *Not rated*	NR	From population-based screening project; identified as high risk	Mean age: DM2: 62.3y ± 5.9 nonDM2: 64.9y ± 6.2 % Male: DM2: 50 nonDM2: 50 *nonDM2 group was high risk*	NR	NR	55% reported family history of diabetes in each group
Hoorn Study Adriaanse et al, 2004[178] *Fair*	NR	From population-based screening project; identified as DM2 From general practices; identified as DM2	Mean age: GPDM: 62.2±7.0 SDM: 63.2±7.3 % Male: GPDM: 49 SDM: 56.9	Educational level: GPDM: 57.1% low, 36.7% middle, 6.1% high SDM: 62.1% low, 30.2% middle, 7.8% high P value = 0.695, ns	Yes	See "other results" column Microalbuminuria (%): GPDM: 26.5 SDM: 20.7 Impaired foot sensitivity (%): GPDM: 51.0 SDM: 46.6 Retinopathy (%): GPDM: 2.0 SDM: 8.6 Lipid lowering med (%): GPDM: 16.3 SDM: 17.2
Hoorn Study Adriaanse et al, 2004[180] *Fair*	NR	From population-based screening project; identified as high risk	Race: >99% Caucasian Mean age: DM2: 63.2 ± 7.3 nonDM2: 62.2 ± 7.3 % Male: DM2: 56.9 nonDM2: 51 *nonDM group was high risk*	NR	Yes	Parent or sibling with DM2: 43.1% nonDM2: 37.8%

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood pressure (mm Hg)	Other risk factors (CVD, etc)	Measures used
Hoorn Study Adriaanse et al, 2002[181] *Not rated*	FPG (mmol/l) newly-diagnosed: 8.5 (2.3) Non-diabetic: 6.5(0.6)	NR	NR	NonDM2 (N=20): 17 with IFG and 10 with both IFG and IGT BMI: DM2: 28.6 ± 3.5 nonDM2: 27.7 ± 4.1	SRQ - used to identify people in general population at increased risk for DM2 Semistructured interviews examining: In newly-diagnosed DM2: the impact of diabetes, understanding of the test result, perceived severity, sense of control In screened non-diabetics: impact of the test results, intention to change lifestyle Both groups: views on the screening procedure
Hoorn Study Adriaanse et al, 2004[178] *Fair*	See "other results" column	NR	NR	See "other results" column BMI: GPDM: 29.5±6.1 SDM: 29.7±4.9	SRQ - used to identify people in general population at increased risk for DM2. Type 2 Diabetes Symptom Checklist (DSC-type 2) - measures presence and burden of diabetes-related symptoms Short Form 36 (SF-36) - measures perceived health status Well-Being Questionnaire (WBQ12) - Dutch version, measures emotional well-being
Hoorn Study Adriaanse et al, 2004[180] *Fair*	FPG mmol/L Diabetic: 7.3 (1.9) Non-diabetic: 5.9 (0.3)	NR	NR	Significant differences in BMI between groups: DM2: 29 + 5.1 vs nonDM2: 27.9 + 4.0, (p=0.045)	SRQ - used to identify people in general population at increased risk for DM2 12-item Well-being Questionnaire (WBQ12) - Dutch version Medical Outcomes Study Short Form 36 (SF-36)

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Intervention	Primary endpoint(s)	Outcomes for standardized measures	Adherence withdrawals (%)
Hoorn Study Adriaanse et al, 2002[181] *Not rated*	Qualitative study Semi-structured interviews specific to intervention or control groups: Newly-diagnosed diabetes group: 30-60 minutes at their home Non-diabetic group: 15-30 minutes via telephone	Psychological impact	Screening procedure: both DM2 and nonDM2 participants evaluated screening procedure as positive and not burdensome 1 person alarmed by diagnosis, the 19 others were not Having diabetes was not experienced as a severe disease, no concerns were expressed	0
Hoorn Study Adriaanse et al, 2004[178] *Fair*	Completed standardized questionnaires at 2w, 6m, and 1y following DM2 positive test result	HRQoL, including: presence and burden of diabetes-related symptoms, perceived health status, emotional well-being	DSC-type 2 score (higher scores indicate more symptom distress) improved significantly within GPDM across follow-up (2w: 0.56; 6m: 0.21; 1y: 0.26, p<0.001), but not for SDM group (2w: 0.24; 6m: 0.24; 1y: 0.29, p=0.093) GPDM consistently worse mean scores on all SF-36 mental health subscales and all WBQ12 scores at each time point compared with SDM Differences were statistically significant (worse) for GPDM group on SF-36 for Role Emotional (F=5.2, p=0.024), Mental Health (F=5.0, p=0.027), and Vitality (F=3.9,p=0.049); Significantly lower Mental Health Component Score for GPDM (F=7.0, p=0.009); Differences were statistically significant (worse) for GPDM group on WBQ12 for General well-being (p=0.048) No differences between groups over time for other dimensions of SF-36 and WB12 SF-36 General Health (F=3.7, p=0.028) and Vitality (F=4.5, p=0.012) scores of GPDM improved significantly over time compared with SDM	GPDM: started with 71, data for 49 SDM: started with 217, data for 116
Hoorn Study Adriaanse et al, 2004[180] *Fair*	Completed standardized questionnaires at 2w, 6m, and 1y following test result (DM2 diagnosis or not)	Psychological well-being Perceived health status	2w after diagnosis: no significant mean differences in psychological well-being nor perceived health status 6m after diagnosis: significantly lower scores of DM2 group for Role Physical (mean difference -8.2 [95% CI -16.2; -0.1], p=0.046) and Role Emotional (mean difference -7.9 [95% CI -15.3; -0.5], p=0.038) dimensions of perceived health status; no other significant differences 1y after diagnosis: no significant mean differences in psychological well-being nor perceived health status	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Other results	Comments	Funding
Hoorn Study Adriaanse et al, 2002[181] *Not rated*	Listed, but not standardized	When capillary glucose > 99 mg/dl (>5.5 mmol/L), venous FPG was measured and within 2w, a 75-g OGTT performed Used WHO (1998) criteria (requiring FPG ≥126 mg/dl (≥ 7.0 mmol/L) on 2 separate occasions, or abnormal OGTT, with 2-h plasma glucose ≥200 mg/dl (≥ 11.1 mmol/L)	Health and Research Development Council of The Netherlands
Hoorn Study Adriaanse et al, 2004[178] *Fair*	General practitioners reported that 76% (31/41) of newly diagnosed GPDM group were detected because of distinct diabetes-related symptoms Baseline significant differences: *GPDM higher*: fasting plasma glucose (mmol/L) 9.7±3.1 vs. 8.5±2.0, p=0.005 A1c (%) 9.1±2.3 vs. 6.7±1.4, p<0.001 Oral blood glucose lowering agents (%) 77.6 vs. 24.1, p<0.001 *SDM higher*: Overweight (BMI ≥ 25)(%) 72.9 vs. 88.8, p=0.011 Hypertension (%) 59.2 vs. 75.0, p=0.042	WHO (1998) criteria used for diagnosis First study to compare these 2 groups	NR
Hoorn Study Adriaanse et al, 2004[180] *Fair*	None	Significant differences in BMI: DM2 29 ± 5.1 vs. nonDM2 27.9 ± 4.0, (p=0.045) Use of antihypertensive drugs: DM2 36.2% vs. nonDM2 35.7%, NS.	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design	Purpose of study	Country; Setting; Year(s) of study	Treatment groups; Sample size	Length of follow-up	Inclusion criteria
Hoorn Study Adriaasne et al, 2005[179] *Fair*	Cohort with comparison (nondiabetic) group	To determine level of diabetes-related symptom distress and its association with negative mood in population-based screening program, comparing DM2 vs nonDM2 (but high risk) groups	Netherlands, Hoorn region	246 DM2: 116 nonDM2: 130	2w 6m 1y	Participant in Hoorn screening project and chosen to be part of this study With DM2 or elevated risk of DM2 (SRQ score > 6) Ages 50-75
Nichols et al, 2004[185] *Poor*	Cohort with comparison (nondiabetic) group	To examine functional health status prior to diagnosis of DM2, and measure effect on functional health status of receiving the diagnosis	United States Kaiser Permanente Northwest, Portland, Oregon	Those meeting new diagnostic criteria (I): 498 Comparison group (C): 589 Originally 1014 in each group, response rate of 69%, missing items lead to final numbers (44%) N=273	1y	Members of HMO Kaiser Permanente Northwest In Kaiser records, but not in diabetes registry, that meet new criteria for diabetes since ADA lowered diagnosis criteria from 140 to 128 mg/dl (7.8 to 7.0 mmol/l) (soon to be diagnosed) Age and gender match comparison group without DM2

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Exclusion criteria	Participant selection	Population	SES or educational level	Pre-existing depression, anxiety analyzed, etc	Existing vascular disease
Hoorn Study Adriaasne et al, 2005[179] *Fair*	NR	From population-based screening project, identified as high risk or DM2	Mean age: DM2: 63.2y ± 7.3y nonDM2: 61.9y ± 7.3y % Male: DM2: 56.9 nonDM2: 50.8 Race: >99% Caucasian	NR	Yes	NR
Nichols et al, 2004[185] *Poor*	Previously diagnosed DM2	Electronic registry database DM2 vs nonDM2	Mean age: 66.9y + 10.5y % Male: 56	NR	Yes	Self report: Hypertension (p<0.001) I: 61.6% C:38.7% Heart problems (p<0.001) I: 40.5% C: 23.5% Neuropathy symptoms (p=0.003) I: 30.7% C: 22.5% Diabetes symptoms I: 55.1% C: 47.8%

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood pressure (mm Hg)	Other risk factors (CVD, etc)	Measures used
Hoorn Study Adriaasne et al, 2005[179] *Fair*	FPG (mmol/l) Diabetic: 7.3 (1.9) Non-diabetic: 5.9 (0.3)	NR	NR	BMI (kg/m^2): DM2: 29.0±5.1 nonDM2: 28.0±4.0	SRQ - used to identify people in general population at increased risk for DM2 Diabetes Type 2 Symptom Checklist (DSC-type 2) Negative Well-being (NWB) Subscale of Well-being questionnaire (WBQ12) - Dutch version
Nichols et al, 2004[185] *Poor*	NR	NR	NR	Self report: Depression I: 14.1% C: 13.4% BMI (p<0.001) I: 30.3% C: 27.9%	SF-12 Health Survey Physical component (PCS-12) Mental component (MCS-12)

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Intervention	Primary endpoint(s)	Outcomes for standardized measures	Adherence withdrawals (%)
Hoorn Study Adriaasne et al, 2005[179] *Fair*	Completed standardized questionnaires at 2w, 6m, and 1y following DM2 Screening test Analyzed all variables	Diabetes-related symptom distress Negative mood	Screening-detected DM2 patients reported significantly greater burden of hyperglycemic (F = 6.0, p=0.015) and of fatigue (F = 5.3, p=0.023) symptoms in the 1st y following diagnosis; outcomes did not change over time, no significant group by time interactions were found Total symptom distress (range 0-4) relatively low for both DM2 (median at 2w, 6m, and 1y; 0.24, 0.24, 0.29) and nonDM2 (0.15, 0.15, 0.18) and not significantly different No average difference and change over time in negative well-being Negative well-being significantly positively related with the total symptom distress score (regression coefficient beta = 2.86, 95% CI 2.15-3.58)	DM2: started with 156; data for 116 (74%) nonDM2: started with 163; data for 130 (80%)
Nichols et al, 2004[185] *Poor*	After ADA reduced fasting glucose level for diagnosing diabetes from 140 to 126 mg/dl (7.8 to 7.0 mmol/l) in 1998, searched Kaiser Permanente Northwest database back to 1994 (database started in 1988) identifying members who were not currently in diabetes registry, but that met new criteria (before diagnosis group) and added an age and gender-matched comparison group Measured functional health status 1y before and 1y after diagnosis of DM2	Functional status	Between-group at baseline: Prior to diagnosis, physical functioning already lower in subjects who met the new criteria than comparisons (39.5 vs. 42.1, p<0.001); Mental functioning was ns (51.4 vs. 51.9, p=0.406) Within-group after 1y: Among those who newly met diagnostic criteria, no difference in change in health status (mental or physical) in those who reported receiving a diagnosis (n=105) compared with those who did not (n=168). Adjusted for age difference (at 1y follow-up) between those receiving diagnosis (younger) and those not (67.0 vs. 69.6, p=0.031); After adjustment for age, learning of diagnosis was not associated with any difference in functional status on either questionnaire or with a change in physical (1.55 vs. 0.05, p=0.233) or mental (-0.63 vs. 0.01, p=0.598) health status compared to those who had not been told of their diagnosis	1y later: Sent out 706 follow-up questionnaires, 623 were still members, received 273 (44%) usable responses

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Other results	Comments	Funding
Hoorn Study Adriaasne et al, 2005[179] *Fair*	None		NR
Nichols et al, 2004[185] *Poor*	Those meeting new criteria were more likely to report: Hypertension (61.6 vs. 38.7%, p<0.001) Heart problems (40.5 vs. 23.5%, p<0.001) Neuropathy symptoms (30.7 vs. 22.5, p=0.003) Diabetes symptoms (55.1 vs. 47.8%, p<0.019) Higher BMI (30.3 vs. 27.9, p<0.001)	Adjusted for age difference at 1y follow-up	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Study design	Purpose of study	Country; Setting; Year(s) of study	Treatment groups; Sample size	Length of follow-up	Inclusion criteria
Peel et al, 2004[186] *Not rated*	Cross-sectional	To assess impact of DM2 new diagnosis on emotions and views	United Kingdom, Scotland Multicenter (16 different practices and 3 hospitals)	40	No follow-up	Newly diagnosed from range of backgrounds (poor, affluent, rural, urban) from various practices and hospitals across Lothian region in Scotland Based within Local Health Care Co-operatives
Skinner et al, 2005[187] *Not rated*	Cross-sectional (1 time assessment at screening)	To assess impact of diabetes screening on anxiety levels in ethnically mixed population	United Kingdom, Leicestershire	1,339 1,189 (complete data sets)	No follow-up	Participant in Screening those at Risk (STAR) study Ages 25-75 (40-75 if White) with $\geq$ 1 risk factor: Known CHD, known risk of CHD or on CHD register, documented history of hypertension with medication, cerebrovascular disease and/or peripheral vascular disease, diagnosis of IGT or IFG, women with polycystic ovary syndrome and obesity (BMI > 25 or > 23 kg/m^2 in South Asians, BMI > 30 kg/m^2, BMI > 25 kg/m^2 with sedentary lifestyle), women with previous history of gestational disease, first-degree relative with DM2

Abbreviations: ADA, American Diabetes Association; ADDITION Study, Anglo-Danish-Dutch Study of Intensive Treatment and Complication Prevention in Type 2 Diabetic Patients Identified by Screening in Primary Care; BG, blood glucose; BMI, body mass index; C, control group; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes; DM2, type 2 diabetes mellitus; DSC-Type 2, Diabetes Symptom Checklist - Type 2 diabetes; FBG, fasting blood glucose; FPG, fasting plasma glucose; GPDM, general practice-diagnosed diabetes; HADS, Hospital Anxiety and Depression Scale; HAI, Health Anxiety Inventory; HDL, high density lipoprotein; HMO, Health Maintenance Organization; HRQoL, Health Related Quality of Life questionnaire; I, intervention group; IF, intensive follow-up group; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LF, limited follow-up group; m, months; MCS, Mental Component Score; NA, not applicable; nonDM, without diabetes; NR, not reported; NS, not significant; NSD, no significant difference; NWB, negative well-being subscale; OGTT, oral glucose tolerance test; PCS, Physical Component Score; SD, standard deviation; SDM, screening-detected diabetes; SES, socioeconomic status; SF, short form; SRQ, Symptom Risk
Questionnaire; SSAI-SF, Spielburger State-Trait Anxiety Inventory-Short Form; STAR, Screening those at Risk; TC, total cholesterol; w, week; WBQ-12, Well-being Questionnaire-12; WHO, World Health Organization; y, years.

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Exclusion criteria	Participant selection	Population	SES or educational level	Pre-existing depression, anxiety analyzed, etc	Existing vascular disease
Peel et al, 2004[186] *Not rated*	NR	Recruitment from general practitioners and hospitals	Age (mean [range]): 48y (21-77y) 52.5% male 47.5% female	Number of participants (using Registrar General's classification system): Social classes I-II: 10 Social classes III non-manual: 12 Social class III manual: 13 Social classes IV-V: 5	NR	Perhaps, but quantitative data NR
Skinner et al, 2005[187] *Not rated*	Housebound Terminal illness Previously diagnosed DM2 Unable to read or complete questionnaire unaided	Identified at high risk of developing DM2 though general practitioner's or cardiovascular team's lists, Coronary Heart Disease register, or through public media recruitment	High risk for DM2 54% male 46% female 21% Asian 75% Caucasian 4% Other Ages: Asian: 51.2y ± 11.2y Caucasian: 60.5y ± 9.9y	NR	NR	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	FBG (mg/dl) A1c (%)	Lipids (mg/dl)	Blood pressure (mm Hg)	Other risk factors (CVD, etc)	Measures used
Peel et al, 2004[186] *Not rated*	NR	NR	NR	Perhaps, but quantitative data NR	In depth interview (not standardized)
Skinner et al, 2005[187] *Not rated*	NR	TC Asian: 197±35mg/l (5.1±0.9 mmol/l) HDL Asian: 46±15mg/l (1.2±0.4 mmol/l) TC Caucasian: 209±46 mg/dl (5.4±1.2 mmol/l) HDL Caucasian: 54±19 mg/dl (1.4±0.5 mmol/l)	Asian: 128 ±21/80±11 mmHg Caucasian: 134±25/80±11 mmHg	Relative with diabetes: Asian: 70% Caucasian: 37% BMI: Asian: 26.88±4.4 kg/m^2 Caucasian: 28.5+5.6 kg/m^2	OGTT to assess diabetes status To access anxiety: SSAI-SF, Emotional Stability Scale of the Big Five Inventory 44, and 3 scales from the Diabetes Illness Representations Questionnaire (modified for interviews)

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Intervention	Primary endpoint(s)	Outcomes for standardized measures	Adherence withdrawals (%)
Peel et al, 2004[186] *Not rated*	In depth interview	Emotional reaction about diagnosis Views about information provision at time of diagnosis	Varied emotional reactions to diagnosis Most wanted detailed information at time of diagnosis	NA
Skinner et al, 2005[187] *Not rated*	Anxiety measured at time of screening	Anxiety	No effect of family history of diabetes ethnic group, or recruitment methods on anxiety 45% of participants reported "little to moderate" amounts of anxiety (mean 35.5, SD 11.6) Emotional stability was significantly (negatively) associated with anxiety (r=-0.45; n=930; p<0.001), with females describing themselves as less emotionally stable than males (t=4.49; df=577; p<0.001) There were no other variables significantly associated with anxiety	NR

APPENDIX B11. EVIDENCE TABLE OF STUDIES EXAMINING ADVERSE EFFECTS OF SCREENING (KQ4)

Study Author, year *Quality rating*	Other results	Comments	Funding
Peel et al, 2004[186] *Not rated*	None	Identified 3 "routes" to diagnosis: 1) Suspected diabetes route 2) Illness route 3) Routine screening route	Scottish Executive Health Department
Skinner et al, 2005[187] *Not rated*	Participants with a first-degree relative with diabetes were more likely to agree that diabetes was hereditary (t=3.22, p<0.001) South Asians were more likely than Caucasians to agree that diabetes is hereditary (t=3.59; p<0.001) and caused by poor medical care (t=4.11; p<0.001), and less likely to agree that it is a chronic condition (t=3.38; p<0.001) 64% of responders thought diabetes was caused by diet 61% of responders thought diabetes was caused by hereditary factors 12% of responders thought that diabetes was serious, shortens life, and causes complications Other outcomes relate to perceived causes of diabetes, duration of diabetes, and impact on diabetes on life	Cannot locate original STAR study <u>Issue with analysis, lost 150 datasets</u>: "Because of problems with recording the ID number on questionnaires, a number of questionnaires could not be linked to results of standardized health assessment. Therefore, where data are reported that combines data from health assessment and the questionnaire, # of participants in analysis is substantially reduced." Authors described ethnically mixed population as 75% Caucasian 21% Asian; 4% Other	NR

Appendix C

Detailed Methods

APPENDIX C1. LITERATURE SEARCH STRATEGIES

Adverse Effects - Overall

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 4 and 5
7 (adverse effect$ or harm or harmed or harming or harms or iatrogen$ or nosocom$ or drug interaction$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 ((Diagnos$ adj5 (Error$ or mistak$)) or (false$ adj3 (positiv$ or negativ$)) or (observer$ adj variation$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 (prejudic$ or bias$ or stigma$ or discriminat$ or unfair$ or illegal$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 ((Stress$ or tension$) adj5 (Psychologic$ or emotion$ or mental$ or family or families or interpersonal$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 (((Life or living) adj3 (Chang$ or style$)) or lifestyl$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 7 or 8 or 9 or 10 or 11
13 4 and 12

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, abstract, full text, keywords, caption text])
2 (prediabet$ or pre-diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, abstract, full text, keywords, caption text]
6 4 and 5
7 (adverse effect$ or harm or harmed or harming or harms or iatrogen$ or nosocom$ or drug interaction$).mp. [mp=title, abstract, full text, keywords, caption text]
8 ((Diagnos$ adj5 (Error$ or mistak$)) or (false$ adj3 (positiv$ or negativ$)) or (observer$ adj variation$)).mp. [mp=title, abstract, full text, keywords, caption text]
9 (prejudic$ or bias$ or stigma$ or discriminat$ or unfair$ or illegal$).mp. [mp=title, abstract, full text, keywords, caption text]
10 ((Stress$ or tension$) adj5 (Psychologic$ or emotion$ or mental$ or family or families or interpersonal$)).mp. [mp=title, abstract, full text, keywords, caption text]
11 (((Life or living) adj3 (Chang$ or style$)) or lifestyl$).mp. [mp=title, abstract, full text, keywords, caption text]
12 7 or 8 or 9 or 10 or 11
13 4 and 12

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, full text, keywords]
2 (prediabet$ or pre-diabet$).mp. [mp=title, full text, keywords]
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, full text, keywords]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, full text, keywords]
6 4 and 5
7 (adverse effect$ or harm or harmed or harming or harms or iatrogen$ or nosocom$ or drug interaction$).mp. [mp=title, full text, keywords])
8 ((Diagnos$ adj5 (Error$ or mistak$)) or (false$ adj3 (positiv$ or negativ$)) or (observer$ adj variation$)).mp. [mp=title, full text, keywords]

9 (prejudic$ or bias$ or stigma$ or discriminat$ or unfair$ or illegal$).mp. [mp=title, full text, keywords]
10 ((Stress$ or tension$) adj5 (Psychologic$ or emotion$ or mental$ or family or families or interpersonal$)).mp. [mp=title, full text, keywords]
11 (((Life or living) adj3 (Chang$ or style$)) or lifestyl$).mp. [mp=title, full text, keywords]
12 7 or 8 or 9 or 10 or 11
13 4 and 12

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, Type 2/
2 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 1 or 2 or 3 or 4
6 (screen$ or diagnos$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed.
9 7 and 8
10 limit 9 to (humans and english language
11 (adverse effect$ or harm or iatrogen$ or nosocom$ or drug interaction$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 exp Diagnostic Errors/
13 (prejudic$ or stigma$ or discriminat$ or unfair$ or illegal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word
14 exp Stress, Psychological/
15 exp Life Change Events/
16 11 or 12 or 13 or 14 or 15
17 5 and 16
18 8 and 17
19 limit 18 to english language
20 limit 19 to humans

Adverse Effects of Treatment – Systematic Reviews

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Hypoglycemic Agents/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
2 exp Sulfonylurea Compounds/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
3 exp Angiotensin-Converting Enzyme Inhibitors/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
4 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
5 (ae or po or to or ct).fs.
6 (adverse effect$ or poison$ or toxic$ or contraindicat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 or 6
8 4 and 7
9 exp Angiotensin II Type 1 Receptor Blockers/ae, po, ct, to
10 8 or 9
11 exp Calcium Channel Blockers/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
12 exp Thiazides/ae, ct [Adverse Effects, Contraindications]
13 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
14 orlistat.mp.

15 7 and 14
16 exp Insulin/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
17 exp Aspirin/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
18 1 or 2 or 3 or 10 or 11 or 12 or 13 or 15 or 16 or 17
19 (systematic$ adj review$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20 (data adj synthesis).tw.
21 (published adj studies).ab.
22 (data adj extraction).ab.
23 meta-analysis/
24 (meta-analy$ or metaanaly$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
25 19 or 20 or 21 or 22 or 23 or 24
26 comment.pt.
27 letter.pt.
28 editorial.pt.
29 Animals/
30 Humans/
31 29 not (29 and 30)
32 18 not 31
33 32 and (19 or 20 or 21 or 22 or 23 or 24)
34 limit 33 to yr="2001 - 2007"

Hemoglobin Alc

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or NIDDM or MODY).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 exp Hemoglobin A, Glycosylated/
6 (hba 1c or a 1c or a1c).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 ((glycat$ or glycosyl$) adj7 (hemoglobin$ or hgb or red blood cell$ or rbc$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 5 or 6 or 7
9 4 and 8
10 ((Diagnos$ adj5 (Error$ or mistake$)) or (false$ adj3 (positiv$ or negativ$)) or (observer$ adj3 variation$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 (sensitivity adj2 specificity).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 (Reproduc$ adj5 (Result$ or outcome$ or reading$ or value$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 (accura$ or reliab$ or prevalen$ or yield$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 10 or 11 or 12 or 13
15 exp Mass Screening/
16 (screen$ or diagnos$ or test$ or detect$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
17 15 or 16
18 9 and 17

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or NIDDM or MODY).mp. [mp=title, abstract, full text, keywords, caption text]

2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, abstract, full text, keywords, caption text]
3 (prediabet$ or pre-diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
4 1 or 2 or 3
5 [exp Hemoglobin A, Glycosylated/]
6 (hba 1c or a 1c or a1c).mp. [mp=title, abstract, full text, keywords, caption text]
7 ((glycat$ or glycosyl$) adj7 (hemoglobin$ or hgb or red blood cell$ or rbc$)).mp. [mp=title, abstract, full text, keywords, caption text]
8 5 or 6 or 7
9 4 and 8
10 ((Diagnos$ adj5 (Error$ or mistake$)) or (false$ adj3 (positiv$ or negativ$)) or (observer$ adj3 variation$)).mp. [mp=title, abstract, full text, keywords, caption text]
11 (sensitivity adj2 specificity).mp. [mp=title, abstract, full text, keywords, caption text]
12 (Reproduc$ adj5 (Result$ or outcome$ or reading$ or value$)).mp. [mp=title, abstract, full text, keywords, caption text]
13 (accura$ or reliab$ or prevalen$ or yield$).mp. [mp=title, abstract, full text, keywords, caption text]
14 10 or 11 or 12 or 13
15 [exp Mass Screening/]
16 (screen$ or diagnos$ or test$ or detect$).mp. [mp=title, abstract, full text, keywords, caption text]
17 15 or 16
18 9 and 17

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, type II/
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Hemoglobin A, Glycosylated/
6 a1c.mp.
7 (glycosyl$ adj7 (hemoglobin$ or hgb or red blood cell$ or rbc$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 5 or 6 or 7
9 4 and 8
10 (systematic adj review$).tw.
11 (data adj synthesis).tw.
12 (published adj studies).ab.
13 (data adj extraction).ab.
14 meta-analysis/
15 comment.pt.
16 letter.pt.
17 editorial.pt.
18 animal/
19 human/
20 18 not (18 and 19)
21 9 not (15 or 16 or 17 or 20)
22 21 and (10 or 11 or 12 or 13 or 14)
23 (200109$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed.
24 22 and 23

Screening

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

2 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 4 and 5

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, abstract, full text, keywords, caption text]
2 (prediabet$ or pre-diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, abstract, full text, keywords, caption text]
6 4 and 5

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
1 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, full text, keywords]
2 (prediabet$ or pre-diabet$).mp. [mp=title, full text, keywords] (0)
3 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, full text, keywords]
4 1 or 2 or 3
5 (screen$ or diagnos$).mp. [mp=title, full text, keywords]
6 4 and 5

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, Type 2/
2 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word
5 1 or 2 or 3 or 4
6 (screen$ or diagnos$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$).ed.
9 7 and 8
10 limit 9 to (humans and english language
11 limit 10 to yr="2004 - 2007"
12 (200109$ or 20011$ or 2002$ or 2003$).ed.
13 9 and 12

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, Type 2/
2 ((fasting glucose or glucose tolerance) adj3 impair$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 ((type 2 or type II or non-insulin dependent) adj3 diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 1 or 2 or 3 or 4
6 (screen$ or diagnos$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$).ed.
9 7 and 8

10 limit 9 to (humans and english language)
11 limit 10 to yr="2004 - 2007"

Treatment

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or MODY or NIDDM).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 Hypoglycemic Agent$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 Glipizide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 Glyburide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 Glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 Metformin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 Rosiglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 Pioglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 Repaglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 Nateglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 Acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor$ or ace inhibitor$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19 (Angiotensin adj3 (block$ or antagon$ or receptor$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
20 (Calcium Channel$ adj3 (antagon$ or Block$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 (antihypertensi$ or anti-hypertensi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 Lovastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 Pravastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27 Fluvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28 Atorvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
29 Rosuvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
30 25 or 26 or 27 or 28 or 29
31 24 or 30
32 4 and 31
33 Antilipemic$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34 Gemfibrozil.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
35 Fenofibrate.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
36 Nicotinic Acid.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
37 Cholestyramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword])
38 Colestipol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39 Colesevelam.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
40 Ezetimibe.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
41 34 or 35 or 36 or 37 or 38 or 39 or 40

42 33 or 41
43 4 and 42
44 Aspirin.mp.
45 4 and 44
46 (Life Style$ or lifestyle$ or ((living or live or lived) adj5 style$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
47 4 and 46
48 Exercis$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
49 (tai chi or tai ji or relaxation or walk$ or yoga or jog or jogging).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword
50 (Physical$ adj3 (Fitness or fit)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
51 48 or 49 or 50
52 4 and 51
53 ((Gastric or stomach) adj3 Bypass$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
54 gastroplast$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
55 ((obese or obesity) adj3 (surger$ or surgic$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
56 53 or 54 or 55
57 4 and 56
58 anti-obesity agent$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
59 ((obese or obesity) adj3 (drug$ or pharmaco$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
60 orlistat.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
61 sibutramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
62 fluoxetine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
63 58 or 59 or 60 or 61 or 62
64 4 and 63
65 Counsel$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
66 4 and 65
67 (Patient$ adj3 (Educat$ or inform$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
68 4 and 67
69 footcare.mp.
70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease$ or ulcer$ or sore$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
72 69 or 70 or 71
73 4 and 72
74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73
75 limit 74 to yr="2001 - 2007"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or MODY or NIDDM).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 Hypoglycemic Agent$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 Glipizide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 Glyburide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 Glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9 Metformin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 Rosiglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 Pioglitazone.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 Repaglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

13 Nateglinide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 Acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor$ or ace inhibitor$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19 (Angiotensin adj3 (block$ or antagon$ or receptor$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
20 (Calcium Channel$ adj3 (antagon$ or Block$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 (antihypertensi$ or anti-hypertensi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 Lovastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 Pravastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27 Fluvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28 Atorvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
29 Rosuvastatin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
30 25 or 26 or 27 or 28 or 29
31 24 or 30
32 4 and 31
33 Antilipemic$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34 Gemfibrozil.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
35 Fenofibrate.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
36 Nicotinic Acid.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
37 Cholestyramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
38 Colestipol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39 Colesevelam.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
40 Ezetimibe.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
41 34 or 35 or 36 or 37 or 38 or 39 or 40
42 33 or 41
43 4 and 42
44 Aspirin.mp.
45 4 and 44
46 (Life Style$ or lifestyle$ or ((living or live or lived) adj5 style$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
47 4 and 46
48 Exercis$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
49 (tai chi or tai ji or relaxation or walk$ or yoga or jog or jogging).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
50 (Physical$ adj3 (Fitness or fit)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword])
51 48 or 49 or 50
52 4 and 51
53 ((Gastric or stomach) adj3 Bypass$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
54 gastroplast$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
55 ((obese or obesity) adj3 (surger$ or surgic$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
56 53 or 54 or 55
57 4 and 56
58 anti-obesity agent$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
59 ((obese or obesity) adj3 (drug$ or pharmaco$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
60 orlistat.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

61 sibutramine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
62 fluoxetine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
63 58 or 59 or 60 or 61 or 62
64 4 and 63
65 Counsel$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
66 4 and 65
67 (Patient$ adj3 (Educat$ or inform$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
68 4 and 67
69 footcare.mp.
70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease$ or ulcer$ or sore$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
72 69 or 70 or 71
73 4 and 72
74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73
75 limit 74 to yr="2001 - 2007"

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or MODY or NIDDM).mp. [mp=title, abstract, full text, keywords, caption text]
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, abstract, full text, keywords, caption text]
3 (prediabet$ or pre-diabet$).mp. [mp=title, abstract, full text, keywords, caption text]
4 1 or 2 or 3
5 Hypoglycemic Agent$.mp. [mp=title, abstract, full text, keywords, caption text]
6 Glipizide.mp. [mp=title, abstract, full text, keywords, caption text]
7 Glyburide.mp. [mp=title, abstract, full text, keywords, caption text]
8 Glimepiride.mp. [mp=title, abstract, full text, keywords, caption text]
9 Metformin.mp. [mp=title, abstract, full text, keywords, caption text]
10 Rosiglitazone.mp. [mp=title, abstract, full text, keywords, caption text]
11 Pioglitazone.mp. [mp=title, abstract, full text, keywords, caption text]
12 Repaglinide.mp. [mp=title, abstract, full text, keywords, caption text]
13 Nateglinide.mp. [mp=title, abstract, full text, keywords, caption text]
14 Acarbose.mp. [mp=title, abstract, full text, keywords, caption text]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor$ or ace inhibitor$).mp. [mp=title, abstract, full text, keywords, caption text]
19 (Angiotensin adj3 (block$ or antagon$ or receptor$)).mp. [mp=title, abstract, full text, keywords, caption text]
20 (Calcium Channel$ adj3 (antagon$ or Block$)).mp. [mp=title, abstract, full text, keywords, caption text]
21 (antihypertensi$ or anti-hypertensi$).mp. [mp=title, abstract, full text, keywords, caption text]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase$.mp. [mp=title, abstract, full text, keywords, caption text]
25 Lovastatin.mp. [mp=title, abstract, full text, keywords, caption text]
26 Pravastatin.mp. [mp=title, abstract, full text, keywords, caption text]
27 Fluvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
28 Atorvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
29 Rosuvastatin.mp. [mp=title, abstract, full text, keywords, caption text]
30 25 or 26 or 27 or 28 or 29
31 24 or 30
32 4 and 31
33 Antilipemic$.mp. [mp=title, abstract, full text, keywords, caption text]
34 Gemfibrozil.mp. [mp=title, abstract, full text, keywords, caption text]
35 Fenofibrate.mp. [mp=title, abstract, full text, keywords, caption text]
36 Nicotinic Acid.mp. [mp=title, abstract, full text, keywords, caption text]

37 Cholestyramine.mp. [mp=title, abstract, full text, keywords, caption text]
38 Colestipol.mp. [mp=title, abstract, full text, keywords, caption text]
39 Colesevelam.mp. [mp=title, abstract, full text, keywords, caption text]
40 Ezetimibe.mp. [mp=title, abstract, full text, keywords, caption text]
41 34 or 35 or 36 or 37 or 38 or 39 or 40
42 33 or 41
43 4 and 42
44 Aspirin.mp.
45 4 and 44
46 (Life Style$ or lifestyle$ or ((living or live or lived) adj5 style$)).mp. [mp=title, abstract, full text, keywords, caption text]
47 4 and 46
48 Exercis$.mp. [mp=title, abstract, full text, keywords, caption text]
49 (tai chi or tai ji or relaxation or walk$ or yoga or jog or jogging).mp. [mp=title, abstract, full text, keywords, caption text]
50 (Physical$ adj3 (Fitness or fit)).mp. [mp=title, abstract, full text, keywords, caption text]
51 48 or 49 or 50
52 4 and 51
53 ((Gastric or stomach) adj3 Bypass$).mp. [mp=title, abstract, full text, keywords, caption text]
54 gastroplast$.mp. [mp=title, abstract, full text, keywords, caption text]
55 ((obese or obesity) adj3 (surger$ or surgic$)).mp. [mp=title, abstract, full text, keywords, caption text]
56 53 or 54 or 55
57 4 and 56
58 anti-obesity agent$.mp. [mp=title, abstract, full text, keywords, caption text]
59 ((obese or obesity) adj3 (drug$ or pharmaco$)).mp. [mp=title, abstract, full text, keywords, caption text]
60 orlistat.mp. [mp=title, abstract, full text, keywords, caption text]
61 sibutramine.mp. [mp=title, abstract, full text, keywords, caption text]
62 fluoxetine.mp. [mp=title, abstract, full text, keywords, caption text]
63 58 or 59 or 60 or 61 or 62
64 4 and 63
65 Counsel$.mp. [mp=title, abstract, full text, keywords, caption text]
66 4 and 65
67 (Patient$ adj3 (Educat$ or inform$)).mp. [mp=title, abstract, full text, keywords, caption text]
68 4 and 67
69 footcare.mp.
70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease$ or ulcer$ or sore$)).mp. [mp=title, abstract, full text, keywords, caption text]
72 69 or 70 or 71
73 4 and 72
74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:
1 ((Diabet$ adj3 (type II or type 2 or non-insulin depend$)) or MODY or NIDDM).mp. [mp=title, full text, keywords]
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, full text, keywords]
3 (prediabet$ or pre-diabet$).mp. [mp=title, full text, keywords]
4 1 or 2 or 3
5 Hypoglycemic Agent$.mp. [mp=title, full text, keywords]
6 Glipizide.mp. [mp=title, full text, keywords]
7 Glyburide.mp. [mp=title, full text, keywords]
8 Glimepiride.mp. [mp=title, full text, keywords]
9 Metformin.mp. [mp=title, full text, keywords]
10 Rosiglitazone.mp. [mp=title, full text, keywords]
11 Pioglitazone.mp. [mp=title, full text, keywords]
12 Repaglinide.mp. [mp=title, full text, keywords]

13 Nateglinide.mp. [mp=title, full text, keywords]
14 Acarbose.mp. [mp=title, full text, keywords]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 (Angiotensin Converting Enzyme Inhibitor$ or ace inhibitor$).mp. [mp=title, full text, keywords]
19 (Angiotensin adj3 (block$ or antagon$ or receptor$)).mp. [mp=title, full text, keywords]
20 (Calcium Channel$ adj3 (antagon$ or Block$)).mp. [mp=title, full text, keywords)
21 (antihypertensi$ or anti-hypertensi$).mp. [mp=title, full text, keywords]
22 18 or 19 or 20 or 21
23 4 and 22
24 Hydroxymethylglutaryl CoA Reductase$.mp. [mp=title, full text, keywords]
25 Lovastatin.mp. [mp=title, full text, keywords]
26 Pravastatin.mp. [mp=title, full text, keywords]
27 Fluvastatin.mp. [mp=title, full text, keywords]
28 Atorvastatin.mp. [mp=title, full text, keywords]
29 Rosuvastatin.mp. [mp=title, full text, keywords]
30 25 or 26 or 27 or 28 or 29
31 24 or 30
32 4 and 31
33 Antilipemic$.mp. [mp=title, full text, keywords]
34 Gemfibrozil.mp. [mp=title, full text, keywords]
35 Fenofibrate.mp. [mp=title, full text, keywords]
36 Nicotinic Acid.mp. [mp=title, full text, keywords]
37 Cholestyramine.mp. [mp=title, full text, keywords]
38 Colestipol.mp. [mp=title, full text, keywords]
39 Colesevelam.mp. [mp=title, full text, keywords]
40 Ezetimibe.mp. [mp=title, full text, keywords]
41 34 or 35 or 36 or 37 or 38 or 39 or 40
42 33 or 41
43 4 and 42
44 Aspirin.mp.
45 4 and 44
46 (Life Style$ or lifestyle$ or ((living or live or lived) adj5 style$)).mp. [mp=title, full text, keywords]
47 4 and 46
48 Exercis$.mp. [mp=title, full text, keywords]
49 (tai chi or tai ji or relaxation or walk$ or yoga or jog or jogging).mp. [mp=title, full text, keywords]
50 (Physical$ adj3 (Fitness or fit)).mp. [mp=title, full text, keywords]
51 48 or 49 or 50
52 4 and 51
53 ((Gastric or stomach) adj3 Bypass$).mp. [mp=title, full text, keywords]
54 gastroplast$.mp. [mp=title, full text, keywords]
55 ((obese or obesity) adj3 (surger$ or surgic$)).mp. [mp=title, full text, keywords]
56 53 or 54 or 55
57 4 and 56
58 anti-obesity agent$.mp. [mp=title, full text, keywords]
59 ((obese or obesity) adj3 (drug$ or pharmaco$)).mp. [mp=title, full text, keywords]
60 orlistat.mp. [mp=title, full text, keywords]
61 sibutramine.mp. [mp=title, full text, keywords]
62 fluoxetine.mp. [mp=title, full text, keywords]
63 58 or 59 or 60 or 61 or 62
64 4 and 63
65 Counsel$.mp. [mp=title, full text, keywords]
66 4 and 65
67 (Patient$ adj3 (Educat$ or inform$)).mp. [mp=title, full text, keywords]
68 4 and 67

69 footcare.mp.
70 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
71 ((foot or feet or toe or toes or heel or plantar) adj5 (disease$ or ulcer$ or sore$)).mp. [mp=title, full text, keywords]
72 69 or 70 or 71
73 4 and 72
74 17 or 23 or 32 or 43 or 45 or 47 or 52 or 57 or 64 or 66 or 68 or 73

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, type II/
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Hypoglycemic Agents/
6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 exp Angiotensin-Converting Enzyme Inhibitors/
19 exp Angiotensin II/
20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
21 19 and 20
22 exp Angiotensin II Type 1 Receptor Block
23 21 or 22
24 exp Calcium Channel Blockers/
25 exp antihypertensive agents/
26 18 or 23 or 24 or 25
27 4 and 26
28 exp Hydroxymethylglutaryl CoA Reductases/
29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34 29 or 30 or 31 or 32 or 33
35 28 or 34
36 4 and 35
37 exp Antilipemic Agents/
38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 38 or 39 or 40 or 41 or 42 or 43 or 44
46 37 or 45

47 4 and 46
48 exp Aspirin/
49 4 and 48
50 exp Life Style/
51 4 and 50
52 exp Exercise/ or exp Exercise Movement Techniques/
53 exp Physical Fitness/
54 52 or 53
55 4 and 54
56 exp Gastric Bypass/
57 exp gastroplasty/
58 exp obesity/su
59 56 or 57 or 58
60 4 and 59
61 exp anti-obesity agents/
62 exp obesity/dt
63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
66 61 or 62 or 63 or 64 or 65
67 4 and 66
68 exp Counseling/
69 4 and 68
70 exp Patient Education/
71 4 and 70
72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapeutic Use]
73 footcare.mp.
74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
75 72 or 73 or 74
76 4 and 75
77 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$).ed.
78 17 and 77
79 27 and 77
80 36 and 77
81 47 not 36
82 77 and 81
83 49 and 77
84 51 and 77
85 55 and 77
86 60 and 77
87 67 and 77
88 69 and 77
89 71 and 77
90 76 and 77
91 randomized controlled trial.pt.
92 controlled clinical trial.pt.
93 randomized controlled trials/
94 random allocation/
95 double-blind method/
96 single blind method/
97 91 or 92 or 93 or 94 or 95 or 96
98 animal/ not human/
99 97 not 98
100 clinical trial.pt.
101 (clinic$ adj25 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

102 exp Clinical Trials/
103 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
104 exp Placebos/
105 placebo$.mp.)
106 random$.mp.
107 Research Design/
108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110 109 not 98
111 110 not 99
112 99 or 111
113 78 and 112
114 79 and 112
115 80 and 112
116 82 and 112
117 83 and 112
118 84 and 112
119 85 and 112
120 86 and 112
121 87 and 112
122 88 and 112
123 89 and 112
124 90 and 112
125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124
126 limit 125 to english language
127 limit 125 to abstracts
128 126 or 127
129 limit 128 to yr="2001 - 2007"

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, type II/
2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word])
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Hypoglycemic Agents/
6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 exp Angiotensin-Converting Enzyme Inhibitors/
19 exp Angiotensin II/
20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
21 19 and 20
22 exp Angiotensin II Type 1 Receptor Blockers/
23 21 or 22

24 exp Calcium Channel Blockers/
25 exp antihypertensive agents/
26 18 or 23 or 24 or 25
27 4 and 26
28 exp Hydroxymethylglutaryl CoA Reductases/
29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34 29 or 30 or 31 or 32 or 33
35 28 or 34
36 4 and 35
37 exp Antilipemic Agents/
38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 38 or 39 or 40 or 41 or 42 or 43 or 44
46 37 or 45
47 4 and 46
48 exp Aspirin/
49 4 and 48
50 exp Life Style/
51 4 and 50
52 exp Exercise/ or exp Exercise Movement Techniques/
53 exp Physical Fitness/
54 52 or 53
55 4 and 54
56 exp Gastric Bypass/
57 exp gastroplasty/
58 exp obesity/su
59 56 or 57 or 58
60 4 and 59
61 exp anti-obesity agents/
62 exp obesity/dt
63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
66 61 or 62 or 63 or 64 or 65
67 4 and 66
68 exp Counseling/
69 4 and 68
70 exp Patient Education/
71 4 and 70
72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapeutic Use]
73 footcare.mp.
74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
75 72 or 73 or 74
76 4 and 75
77 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$).ed.
78 17 and 77

79 27 and 77
80 36 and 77
81 47 not 36
82 77 and 81
83 49 and 77
84 51 and 77
85 55 and 77
86 60 and 77
87 67 and 77
88 69 and 77
89 71 and 77
90 76 and 77
91 randomized controlled trial.pt.
92 controlled clinical trial.pt.
93 randomized controlled trials/
94 random allocation/
95 double-blind method/
96 single blind method/
97 91 or 92 or 93 or 94 or 95 or 96
98 animal/ not human/
99 97 not 98
100 clinical trial.pt.
101 (clinic$ adj25 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
102 exp Clinical Trials/
103 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word])
104 exp Placebos/
105 placebo$.mp.
106 random$.mp.
107 Research Design/
108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110 109 not 98
111 110 not 99
112 99 or 111
113 78 and 112
114 79 and 112
115 80 and 112
116 82 and 112
117 83 and 112
118 84 and 112
119 85 and 112
120 86 and 112
121 87 and 112
122 88 and 112
123 89 and 112
124 90 and 112
125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 126 limit 125 to english language
127 limit 125 to abstracts
128 126 or 127
129 limit 128 to yr="2001 - 2003"
130 limit 128 to yr="2004 - 2007"

Database: Ovid MEDLINE(R)
Search Strategy:
1 exp Diabetes Mellitus, type II/

APPENDIX C1. LITERATURE SEARCH STRATEGIES

2 (impair$ adj3 (fasting glucose or glucose tolerance)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 (prediabet$ or pre-diabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Hypoglycemic Agents/
6 Glipizide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 Glyburide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 Glimepiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9 Metformin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10 Rosiglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 Pioglitazone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 Repaglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13 Nateglinide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14 Acarbose.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 or 15
17 4 and 16
18 exp Angiotensin-Converting Enzyme Inhibitors/
19 exp Angiotensin II/
20 exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
21 19 and 20
22 exp Angiotensin II Type 1 Receptor Blockers/
23 21 or 22
24 exp Calcium Channel Blockers/
25 exp antihypertensive agents/
26 18 or 23 or 24 or 25
27 4 and 26
28 exp Hydroxymethylglutaryl CoA Reductases/
29 Lovastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30 Pravastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 Fluvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32 Atorvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33 Rosuvastatin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34 29 or 30 or 31 or 32 or 33
35 28 or 34
36 4 and 35
37 exp Antilipemic Agents/
38 Gemfibrozil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 Fenofibrate.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (
40 Nicotinic Acid.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 Cholestyramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42 Colestipol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
43 Colesevelam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
44 Ezetimibe.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 38 or 39 or 40 or 41 or 42 or 43 or 44
46 37 or 45
47 4 and 46
48 exp Aspirin/
49 4 and 48
50 exp Life Style/
51 4 and 50
52 exp Exercise/ or exp Exercise Movement Techniques/
53 exp Physical Fitness/
54 52 or 53
55 4 and 54
56 exp Gastric Bypass/

57 exp gastroplasty/
58 exp obesity/su
59 56 or 57 or 58
60 4 and 59
61 exp anti-obesity agents/
62 exp obesity/dt
63 orlistat.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
64 sibutramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
65 fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
66 61 or 62 or 63 or 64 or 65
67 4 and 66
68 exp Counseling/
69 4 and 68
70 exp Patient Education/
71 4 and 70
72 exp Foot Diseases/nu, pc, dh, dt, rh, su, tu [Nursing, Prevention & Control, Diet Therapy, Drug Therapy, Rehabilitation, Surgery, Therapeutic Use]
73 footcare.mp.
74 ((foot or feet or toe or toes or heel or plantar) adj5 (care or cares or caring or cared)).mp.
75 72 or 73 or 74
76 4 and 75
77 (200109$ or 20011$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$).ed.
78 17 and 77
79 27 and 77
80 36 and 77
81 47 not 36
82 77 and 81
83 49 and 77
84 51 and 77
85 55 and 77
86 60 and 77
87 67 and 77
88 69 and 77
89 71 and 77
90 76 and 77
91 randomized controlled trial.pt.
92 controlled clinical trial.pt.
93 randomized controlled trials/
94 random allocation/
95 double-blind method/
96 single blind method/
97 91 or 92 or 93 or 94 or 95 or 96
98 animal/ not human/
99 97 not 98
100 clinical trial.pt.
101 (clinic$ adj25 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
102 exp Clinical Trials/
103 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
104 exp Placebos/
105 placebo$.mp.
106 random$.mp.
107 Research Design/
108 (latin adj square).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
109 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 10
110 109 not 98

APPENDIX C1. LITERATURE SEARCH STRATEGIES

111 110 not 99
112 99 or 111
113 78 and 112
114 79 and 112
115 80 and 112
116 82 and 112
117 83 and 112
118 84 and 112
119 85 and 112
120 86 and 112
121 87 and 112
122 88 and 112
123 89 and 112
124 90 and 112
125 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124
126 limit 125 to english language
127 limit 125 to abstracts
128 126 or 127
130 limit 128 to yr="2004 - 2007"
131 128 not (129 or 130)

Population

Study participants were aged 18 years or older with DM2 (type 2 diabetes) or prediabetes. Persons labeled as "non-insulin dependent diabetes" were assumed to have DM2. The acceptable diagnostic criteria for DM2 included those of the National Diabetes Data Group Standards,[1] the World Health Organization,[2, 3] or the American Diabetes Association.[4] If the criteria for diagnosis of DM2 were not given in a study, the authors' statement of the diagnosis among participants was accepted.

Prediabetes was defined as either or both of IFG (impaired fasting glucose) or IGT (impaired glucose tolerance).[5] IFG is defined as a fasting plasma glucose ≥ 100 and <126 mg/dl and IGT as random glucose ≥ 140 and <200 mg/dl.[5] The lower threshold for IFG was changed in 2003 from 110 mg/dl to 100 mg/dl;[6] either definition was included in our review.

As the purpose of examining treatment interventions among persons with DM2 was to indirectly address the question of whether knowledge of the diagnosis of diabetes would change clinical management because effective interventions were available after diagnosis, we focused on intervention studies where the populations were either screen-detected or newly diagnosed (defined as a clinical diagnosis in the last 12 months). We felt that examination of persons with diabetes for short duration was important as the lower glycemic levels and rates of cardiovascular risk factors among these persons were more readily extrapolated to a screen-detected population. For intervention studies comparing DM2 to nondiabetic populations, we did not restrict duration of disease as we wanted to determine if there were any differences in treatment approaches between these two populations.

Setting

As in most USPSTF (US Preventive Services Task Force reviews),[7] we focused on traditional primary care settings as well as other clinical settings where general populations obtain primary care (e.g., urgent care facilities, emergency rooms, nursing homes, work-site and school clinics, etc.). Interventions involved a variety of health care providers, including physicians, dieticians, nurses, and other ancillary staff. In-patient interventions and interventions delivered by specialty providers were, in general, excluded. However, large and important clinical trials that were delivered by specialists were included if we felt that the intervention could also be delivered in the primary care setting. We felt that such critical studies must be considered as part of the body of evidence upon which to make recommendations.

Study Design

For Key Questions examining direct evidence for screening programs and the adverse effects of screening (Key Questions #1 and #4), we included studies of any design as we anticipated a paucity of trial evidence and we wanted to examine as broad a literature as possible. We confined our review of intervention effectiveness (Key Questions #2 and #3) to RCTs (randomized controlled trials) and controlled clinical trials, the latter defined as studies where the

investigator assigned exposure to the intervention in a non-randomized fashion. There is a large volume of literature on the efficacy and effectiveness of diabetes treatments and we therefore chose to limit our review of treatment interventions to study designs with the lowest inherent risk of bias.

We focused generally on placebo or usual care comparators, rather than active-control or head-to-head trials. Studies comparing one treatment approach to another among persons with DM2 do not inform the question of whether it is beneficial to have knowledge of whether a person has diabetes or not. For example, studies were excluded that compared one insulin regime to another. Similarly, diet and physical activity counseling interventions were excluded if they compared one type of diet or counseling approach to another. However, for studies comparing diabetic to nondiabetic populations, we also included head-to-head trials as they inform the question of whether persons with diabetes should be treated with different drugs than persons without diabetes.

Adverse effects of treatment (Key Question #5) were reviewed using data from included studies. For interventions that were considered by the authors to be potentially critically important to the decision-making process of the USPSTF, we looked for recent, fair- or high-quality systematic reviews on the adverse effects of these interventions.

Interventions

A variety of treatment interventions were examined in this review (Figure 2, the Analytic Framework) to address the question of whether knowledge of diabetes (either through screening or from clinical presentation) followed by appropriate treatment, would improve health outcomes. All interventions among persons with diabetes were subject to the inclusion criteria of disease duration (either screen-detected or duration $\leq$ 1 year), as discussed above. Person with prediabetes are, by definition, screen-detected, so no duration of disease was relevant for interventions among this population.

For populations with diabetes, we included interventions which focused on treatments for known risk factors for cardiovascular and cerebrovascular disease (hyperlipidemia and hypertension), treatments optimizing glycemic control, the management and prevention of progression of potential diabetes complications (foot care, counseling for improved diet and physical activity levels), and health care system interventions that manage diabetes and related complications and comorbidities (disease management and multicomponent interventions at the system level). We excluded general diabetes education interventions, interventions focused on self-monitoring of blood glucose, interventions focused on optimal medication usage (most commonly insulin), and complementary and alternative medicines and approaches. These interventions were felt to be beyond the scope of the review, they primarily report intermediate outcomes, and their relationship to distal health outcomes is unclear.

For prediabetes, we included interventions which potentially diminish or delay the progression to diabetes, as well as interventions which minimize cardiovascular and cerebrovascular risk factors, including both lifestyle interventions or pharmacotherapy.

Interventions focused on tight versus usual glycemic control in screen-detected DM2 populations or in persons with disease duration ≤ 1 year were included as these interventions indirectly inform the question of whether knowledge of diabetes will alter treatment and therefore improve outcomes. Therapy for different blood pressure and lipid targets were also included in screen-detected or recently diagnosed populations, for similar reasons.

Various comparisons were examined for DM2 treatment studies. We included studies which compared the treatment effect of an intervention in persons with screen-detected DM2 to the effect in persons with clinically-detected diabetes. Studies were also included which compared intervention effect or safety between persons with diabetes and normoglycemic populations. Such studies answer the question as to whether knowledge of diabetes will alter choice of treatment approach. Here we included studies where duration of diabetes was greater than one year or where duration was unknown, recognizing that some caution is needed in extrapolating from populations with longer duration diabetes to screen-detected persons. Comparisons of diabetic and nondiabetic populations across studies were not included in this review as it was considered too difficult to control for potential confounding across studies.

Combination therapy (where both the treatment and control groups received identical therapy [of one or more drugs] in addition to either the study drug or placebo) for glycemic control or for lipid and blood pressure management were also included if participants had diabetes for ≤ 1 year. When an additional drug for a new indication was added to an existing drug treatment regime (e.g., an antihypertensive drug for newly-diagnosed hypertension in a study population already using one or more hypoglycemic agents), these studies were also included, again subject to the inclusion criteria of diagnosis during the last 1 year.

Multicomponent health care system and clinical practice interventions aimed at the primary care setting were included, as long as they reported final health outcomes. In view of the large value of literature available, we used a recent, high-quality systematic review of quality improvement and disease management strategies, updating their literature search (dated April, 2006) using Shojania and colleagues' search strategy.[8]

Studies of diabetes and prediabetes treatments as well as studies of screening interventions that are in progress (i.e., final health outcomes data have not yet been published) at the time of our final searches are presented in tabulated form with the anticipated date of completion. These studies will include persons with diabetes of any duration, as awareness of these studies may be useful to the reader and duration data (if not an inclusion criteria) may not yet be available.

Outcomes

This review focuses primarily on final health outcomes (Figure 2, the Analytic Framework) as the USPSTF does not generally base recommendations on intermediate outcomes. For studies of persons with prediabetes, we examined the intermediate outcome of incidence of DM2, as this outcome is usually a primary one for these studies, and the important and emerging literature on treatment for prediabetes does not, for the most part, yet encompass long-term health outcomes.

The final health outcomes that we examined included cardiovascular morbidity, symptomatic neuropathy, non-healing ulcers, lower extremity amputations, stage IV (glomerular filtration rate 15-29 mg/min) and V (patients on renal replacement therapy or with a glomerular filtration rate of <15 ml/min) chronic kidney disease, severe visual impairment, mortality, and quality of life.

Mathematical Modeling

In the absence of direct evidence on the effectiveness of screening or treatment of newly-diagnosed DM2, researchers have applied mathematical models to attempt to answer these questions. Such models are useful to assess effectiveness and efficiency when trials are infeasible or long-term outcomes are not available.[9] We searched systematically for publications examining the health outcomes of interest to us using models of either screening for DM2 or prediabetes, or treatment of newly-diagnosed DM2. We also consulted experts in the economics of diabetes screening to locate any additional studies.

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APPENDIX C3. U.S. PREVENTIVE SERVICES TASK FORCE QUALITY RATING CRITERIA FOR RCTS AND OBSERVATIONAL STUDIES*

DIAGNOSTIC ACCURACY STUDIES

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

RANDOMIZED CONTROLLED TRIALS (RCTS) AND COHORT STUDIES

Criteria:

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intension-to-treat analysis for RCTs

APPENDIX C3. U.S. PREVENTIVE SERVICES TASK FORCE QUALITY RATING CRITERIA FOR RCTS AND OBSERVATIONAL STUDIES*

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

CASE CONTROL STUDIES

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

*__Reference:__

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APPENDIX C4. QUALITY RATING CRITERIA FOR SYSTEMATIC REVIEWS *

1. Comprehensiveness of sources/search strategy used:
    a. Were search terms reported?
    b. Was the search comprehensive (Medline, search reference lists and/ or experts)?
    c. Were the search terms applicable?

2. Standard appraisal of included studies:
    a. Were inclusion/exclusion criteria reported?
    b. Are criteria valid?

3. Quality/validity assessment:
    a. Were criteria for validity/quality assessment explicit and applied to all studies?
    b. Were quality criteria appropriate (e.g. criteria appropriate for study design)?

4. Analysis/synthesis:
    a. Were methods used to combine studies reported?
    b. Were studies that were combined similar to one another (e.g. appropriate to combine, similar patient populations etc)?

5. Validity of conclusions:
    a. Were conclusions supported by the data?

6. Recency and relevance:
    a. Is the study recent and relevant to scope?

7. Application to practice:
    a. Are your patients largely different from patients in this study?
    b. Is this feasible in your setting?

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APPENDIX C5. EXPERT REVIEWERS

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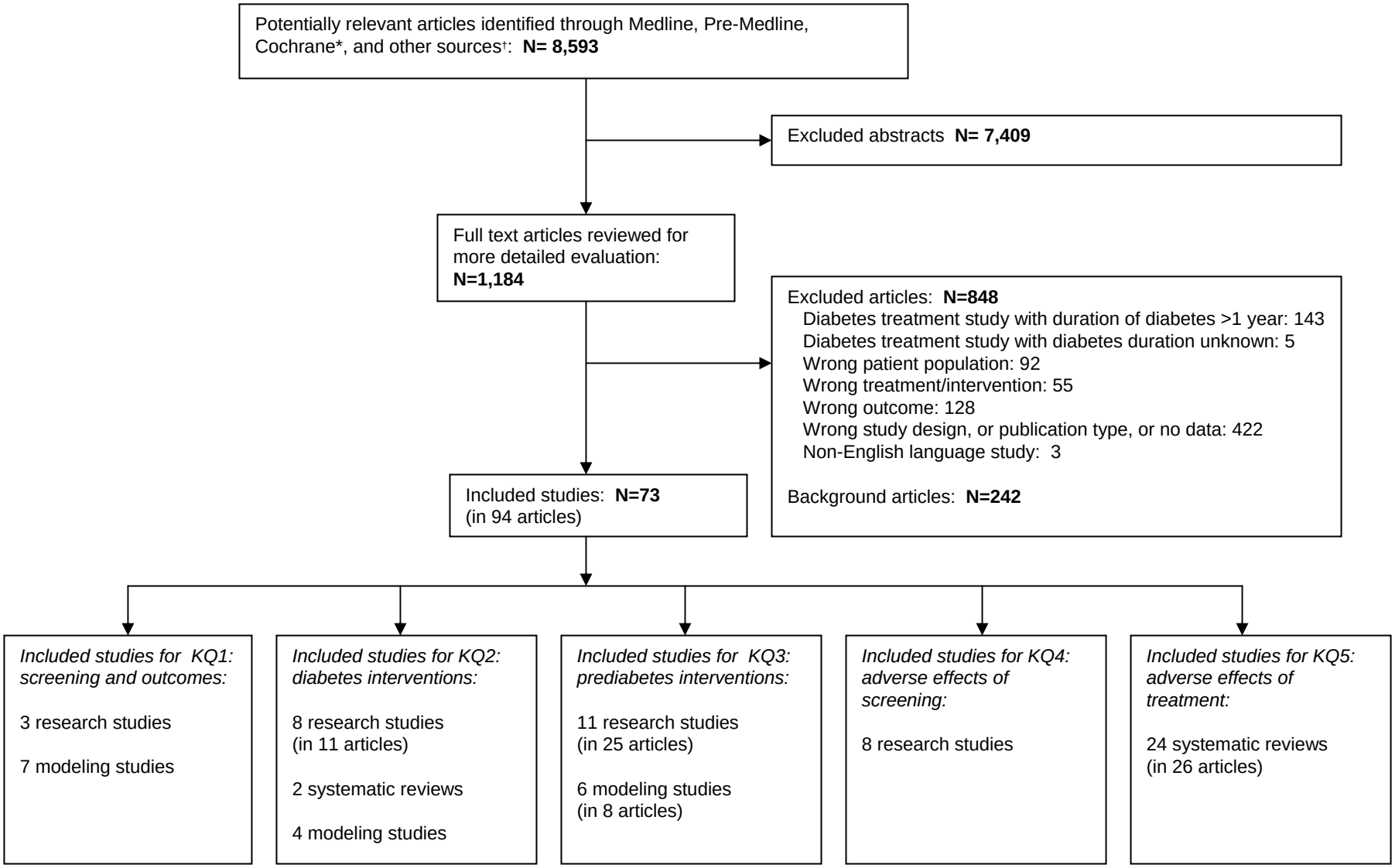
APPENDIX C6. FLOW DIAGRAM OF LITERATURE EVALUATED FOR INCLUSION



*Cochrane Databases include the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness

†Other sources include reference lists and expert referrals

Diabetes Treatment Studies with a Duration of Diabetes > 1 Year

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