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Screening for Type 2 Diabetes Mellitus: Systematic Review to Update the 2008 U.S. Preventive Services Task Force Recommendation

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment.

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Structured Abstract

Background: Type 2 diabetes mellitus (DM) is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness, a major cause of heart disease and stroke, and is the seventh leading cause of death in adults in the United States. Screening could lead to earlier detection and earlier or more intensive treatment of persons with asymptomatic DM, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), potentially resulting in improved clinical outcomes.

Purpose: To systematically update the 2008 U.S. Preventive Services Task Force (USPSTF) review on screening for type 2 diabetes in adults.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through March 2014), and MEDLINE (2007 to March 2014), and manually reviewed reference lists.

Study Selection: Randomized controlled trials, controlled observational studies, and good-quality systematic reviews on benefits and harms of screening for DM, IFG, or IGT versus no screening; treatment versus no treatment; more versus less intensive glucose, blood pressure or lipid control interventions; or aspirin use versus nonuse in persons with DM, IFG, or IGT.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): In one good- and one fair-quality trial screening for DM was associated with no mortality benefit versus no screening, including one trial of patients at higher risk for diabetes (HR 1.06 [95% CI, 0.90 to 1.25]). Evidence on harms of screening was limited, but indicated no long-term psychological harms. Consistent evidence from multiple trials found treatment of IFG/IGT associated with delayed progression to DM. Most trials of treatment for IFG/IGT found no difference in all cause or cardiovascular mortality, though one trial found use of lifestyle modification reduced risk of both outcomes after 23 years followup. For screen-detected diabetes, one large, fair-quality trial found no effect of an intensive multifactorial intervention on risk of all-cause or cardiovascular mortality versus standard control. For established diabetes (not specifically screen-detected), intensive glucose treatment was associated with reduced risk of myocardial infarction and retinopathy, with no effects on mortality. Intensive blood pressure control was associated with a slightly reduced risk of mortality versus standard therapy, but evidence from 2 recent major trials was mixed. Two trials found intensive multifactorial interventions associated with reduced mortality versus standard interventions. Certain pharmacological therapies for screen-detected or early DM, IFG or IGT were associated with increased risk of withdrawal due to adverse events, hypoglycemia, or hypotension, with no increase in risk of serious adverse events.

Limitations: We did not include non-English language articles. Few studies of treatment were conducted in screen-detected populations.

Conclusions: Screening for DM did not improve mortality after 10-years followup and more evidence is needed to determine effective treatments for screen-detected DM. However, treatment for IFG/IGT was associated with delayed progression to DM.

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

Purpose

This report updates a 2008 systematic review on screening for type 2 diabetes mellitus (DM) in adults.[1,2] It will be used by the U.S. Preventive Services Task Force (USPSTF) to update their recommendations on screening for DM.[3] This update focuses on benefits and harms of screening for DM, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT) in adults, and benefits and harms of subsequent treatments for IFG, IGT, or DM. Prenatal screening and screening of children are not addressed in this review.

Previous U.S. Preventive Services Task Force Recommendation

In 2008, the USPSTF recommended screening for DM in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg (B recommendation). Although direct evidence on benefits and harms of screening was not available, the USPSTF recommendation was based on the ability of screening to identify persons with DM and evidence that, in diabetic patients with hypertension, more intensive blood pressure treatment was associated with reduced risk of cardiovascular events, including cardiovascular mortality.

The USPSTF found insufficient evidence to assess the balance of benefits and harms of screening in adults without blood pressure greater than 135/80 mm Hg (I statement). The USPSTF found lifestyle and/or drug interventions in patients with IFG or IGT associated with reduced risk of progression to DM after up to 7 years followup,[4-11] but three trials on the effects of drug and lifestyle interventions in persons with IFG or IGT reported inconsistent effects on cardiovascular outcomes and had some methodological shortcomings.[12-15] The USPSTF also identified a number of evidence gaps:

- No randomized, controlled trials (RCTs) directly addressed the health benefits of either targeted or mass screening for DM, IFG, or IGT.
- Harms of screening were sparsely reported.
- No study directly compared effectiveness of treatments in persons with screen-detected versus clinically-detected DM, and no study evaluated treatment effects in an exclusively screen-detected or recently-diagnosed DM cohort.
- Evidence on harms of treating DM early as a result of screening were not available, however, many systematic reviews examined adverse effects of commonly used DM medications.
- Evidence on screening frequency was limited to modeling studies.

Condition Definition

DM is a metabolic disorder characterized by hyperglycemia. There are two types of DM: type 1, often diagnosed in childhood and characterized by autoimmune destruction of pancreatic islet cells that produce insulin, and type 2 (the focus of this report), characterized by insulin resistance and relative insulin deficiency. Diagnosis of DM, IFG, and IGT is based on measures of glycated hemoglobin (HbA1c), random and fasting blood sugar, or oral glucose tolerance test (OGTT) values, as shown in **Table 1**.[16] DM is defined as HbA1c greater than 6.5 percent, random plasma glucose greater than 200 mg/dL, fasting plasma glucose greater than126 mg/dL, or oral glucose tolerance test after 2 hours greater than 200 mg/dL; parameters for IFG and IGT are HbA1c less than 6.5 with fasting plasma glucose levels of 100 mg/dL to 125 mg/dL, and OGTT values of 140 mg/dL to 199 mg/dL, respectively.[16]

Prevalence and Burden of Disease

In the United States, about 19 million persons were diagnosed with diabetes in 2010, with an estimated 7 million persons undiagnosed; about 90 percent to 95 percent of those have type 2 DM.[17,18] Prevalence of DM increases with age and varies according to sex and race and ethnicity (**Table 2**).[19-21] From 2005 to 2008, the proportion of persons with diagnosed or undiagnosed DM was 4 percent in persons ages 20 to 44 years, 14 percent in persons ages 45 to 64 years, and 27 percent in persons age 65 years and older. In 2010, about one million adults with newly diagnosed DM were between the ages of 45 and 64 years, with 465,000 new cases in younger adults and 390,000 new cases in older adults.[17] In persons younger than age 44 years, similar proportions of men and women are diagnosed with DM; however, prevalence is slightly higher in men in older age groups (**Table 2**). Prevalence varies substantially according to age, ranging from 1 percent to 2 percent in women younger than age 44 years to 22 percent to 41 percent in men older than age 75 years (**Table 2**).[17,19,20] Racial and ethnic groups with the highest risk of diagnosed DM include blacks (rates are 77% higher than whites), Hispanics (rates are 66% higher than whites), and Asians (rates are 18% higher than whites).[17]

Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness in the United States. Diabetes is also a major cause of heart disease and stroke and the seventh leading cause of death in adults.[17] Prevalence of DM in adults in the United States has steadily increased over the past 15 years, rising from about 5 percent in 1995 to 8 percent in 2010.[21] Some racial and ethnic groups are disproportionately affected by complications. For example, blacks and Hispanics are more likely than whites to experience end-stage renal disease,[22] and blacks are almost twice as likely to have amputations of lower extremities.[23] Whites and blacks are more likely to experience diabetes-related heart disease or stroke compared with Hispanics,[24] and blacks, American Indians/Alaska Natives, and Hispanics are more likely to die from DM than whites (age-adjusted death rates 39.5, 34.0, and 25.6 vs. 19.1 per 100,000, respectively).[25]

Etiology and Natural History

DM is caused by insulin resistance, relative insulin deficiency, and inability to maintain normal blood glucose levels. DM typically develops slowly, and progression from normal glycemia to asymptomatic, subclinical disease, and finally to frank DM may take a 10 years or longer.[26,27] However, during the subclinical phase, vascular damage can occur and microvascular disease (e.g., retinopathy and neuropathy) may already be present at the time of DM diagnosis.[16,26]

Risk Factors

Many risk factors are associated with development of DM in adults. Nonmodifiable risk factors include a first-degree relative with DM, a genetic predisposition to insulin resistance, race and ethnicity, and, in women, history of polycystic ovarian syndrome, gestational diabetes, or giving birth to a baby weighing more than 9 pounds.[16,17,19,20,28-30] The risk of developing DM also increases with advancing age (see above).[16,31] Modifiable risk factors for DM include obesity or a high percentage of visceral (abdominal) fat, physical inactivity, smoking, and consumption of a diet high in saturated fat. DM is also frequently associated with other health conditions, such as hyperlipidemia, hypertension, and metabolic syndrome.[16,17,28,32,33]

Rationale for Screening and Screening Strategies

Screening asymptomatic adults for DM may lead to earlier identification and therefore earlier or more intensive treatments to prevent the negative health outcomes associated with DM.[18] Strategies for screening include routine screening, targeted screening based on presence of risk factors, or using risk assessment instruments.

Interventions and Treatment

Lifestyle interventions for glycemic control are considered first-line therapies in most patients and include diet and physical activity or exercise. Numerous drugs from a variety of classes are used to treat DM. These include the biguanide metformin, which lowers glucose production in the liver and is considered a first-line pharmacological treatment for newly diagnosed DM;[34] sulfonylureas (glipizide, glyburide, gliclazide, glimepiride) and meglitinides (repaglinide, nateglinide), which stimulate the pancreas to produce and release more insulin; thiazolidinediones (TZDs) (pioglitazone, rosiglitazone), which make tissues more sensitive to insulin; dipeptidyl peptidase IV inhibitors (sitagliptin, saxagliptin, linagliptin), which increase insulin secretion and reduce sugar production; alpha-glucosidase inhibitors (acarbose, voglibose, miglitol), which block enzymes that help digest starches, slowing the postprandial rise in blood sugar; and insulin.

Patients with high BMI (>35 kg/m^2), persons younger than age 60 years, or women with a history of gestational diabetes may be initially treated with metformin in addition to lifestyle interventions.[16] In addition to treatment of DM, screening for and treatment of other modifiable

diseases that often accompany DM, including dyslipidemia and hypertension, may also be initiated. Other interventions to reduce risk of cardiovascular disease and microvascular complications include blood pressure and lipid-lowering therapy, aspirin, and monitoring and treatments for retinopathy, nephropathy, or neuropathy.[16]

Current Clinical Practice

Screening for DM can be performed by testing fasting plasma glucose (FPG), 2-hour plasma glucose following an OGTT, or HbA1c.[16] Screening with HbA1c is generally more convenient than FPG or OGTT, as pretest fasting is not required and HbA1c is now considered a diagnostic test for DM by the American Diabetes Association (ADA) and the World Health Organization (WHO),[16,35] though there is some evidence suggesting that HbA1c may be less sensitive than FGP or OGTT when using the currently recommended diagnostic cut-point of greater than or equal to 6.5 percent.[36-38] The ADA recommends confirmatory retesting when feasible or in the absence of unequivocal hyperglycemia following initial testing.[16] Following diagnosis of DM, lifestyle, and other interventions are initiated to lower glucose levels and reduce risk of vascular complications (see above). Recent guidelines from the ADA recommend target HbA1c levels of 6.5 percent to 8 percent, depending on the individual patient.[16]

Recommendations of Other Groups

Initial Screening

The ADA[34] recommends screening for DM in persons age 45 years and older and screening those with risk factors regardless of age. Most other groups, including the American Association of Clinical Endocrinologists,[39] the American Academy of Family Physicians,[40] the Australian National Evidence-based Guidelines group,[41] Diabetes UK,[42] and the Canadian Task Force on Preventive Health Care,[43] recommend screening persons with risk factors. Identifying at-risk persons who may warrant screening can be based on the presence of known risk factors or by using DM risk calculators (see Contextual Question 2). In 2002, the WHO concluded there was no direct evidence that individuals benefit from early detection of DM through screening, but stated that health authorities and professional organizations should develop their own screening policies based on individual benefits and costs.[44]

Screening Intervals

For persons with normal initial screening tests, the ADA[34] and Australian National Guidelines[41] recommend rescreening every 3 years. The American Association of Clinical Endocrinologists,[39] ADA,[34] and Australian National Guidelines[41] recommend annual testing of persons initially identified as having IFG or IGT. The Canadian Task Force recommends rescreening either annually or every 3 to 5 years depending on risk level.[43]

Chapter 2. Methods

Key Questions and Analytic Framework

Using established methods,[45] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**).

The key questions are:

1. Is there direct evidence that screening for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance in asymptomatic adults improves health outcomes?
2. What are the harms of screening adults for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?
3. Do interventions for screen-detected or early type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance provide an incremental benefit in health outcomes compared with no interventions or initiating interventions after clinical diagnosis?
4. What are the harms of interventions for screen-detected or early type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?
5. Is there evidence that more intensive glucose, blood pressure, or lipid control interventions improve health outcomes in adults with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance compared with traditional control? Is there evidence that aspirin use improves health outcomes in these populations compared with nonuse?
6. What are the harms of more intensive interventions compared with traditional control in adults with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?
7. Do interventions for impaired fasting glucose or impaired glucose tolerance delay or prevent progression to type 2 diabetes?
8. Do the effects of screening or interventions for screen-detected or early type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance vary by subgroups, such as age, sex, or race and ethnicity?

Four contextual questions were also requested by the USPSTF to help inform the report. Contextual questions are not reviewed using systematic review methodology.[45] Rather, the approach to contextual questions is to focus on evidence from key, high-quality studies.

1. What is the yield (incidence) of starting screening at different ages or rescreening at different intervals in adults with an initial normal fasting blood glucose, HbA1c, or glucose tolerance test?
2. What is the utility of using formal risk calculators versus less formal risk factor assessment (e.g., family history, body mass index) in determining a person's risk for developing diabetes?
3. What is the utility of existing modeling studies of type 2 diabetes screening versus no screening in examining important health outcomes?

4. Is there evidence that intensive blood pressure, lipid lowering, or use of aspirin is more effective in persons with diabetes compared with persons without diabetes?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through March 2014), and Ovid MEDLINE (2007 through March 2014) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). For key questions related to screening, we selected studies of asymptomatic adults without known DM, IFG, or IGT who underwent testing with HbA1c, OGTT, random plasma glucose, or fasting plasma glucose. For key questions related to treatment, we selected studies of adults with screen-detected DM, IFG, or IGT that compared pharmacological interventions for glycemic control or lifestyle interventions versus placebo, no intervention, or usual care. Because few studies specifically enrolled patients with screen-detected DM, we also included studies of patients with early DM (defined as pharmacologically untreated HbA1C less than 8.5% or diagnosis of DM within the last year), who are likely to be more similar to persons identified by screening than those with more advanced or longstanding DM. We excluded studies conducted in pregnant women and children. We included studies on whether more intensive glucose, blood pressure, or lipid control interventions (compared with traditional control) or aspirin use (compared with nonuse) improve health outcomes in adults with DM, IFG, or IGT. For these interventions, we included studies of patients with screen-detected or established DM without an HbA1c or duration restriction, as few trials examined the effects of more versus less intensive therapies for early DM as defined above. Outcomes included all-cause and cardiovascular mortality, cardiovascular morbidity (including myocardial infarction [MI], stroke, congestive heart failure), chronic kidney disease, amputations, skin ulcers, visual impairment (including blindness), periodontitis (including tooth loss), neuropathy, quality of life; and progression from IFG or IGT, to DM. Harms included potential harms of screening such as labeling, anxiety, and false-positive results,[34] as well as harms of treatment. We included randomized, controlled trials, cohort, and case-control studies for all key questions, and relevant systematic reviews that were of good quality and current enough to include critical recent studies. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results and, when appropriate, we contacted study authors

for missing data. Two investigators independently applied criteria developed by the USPSTF[45] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process. When otherwise not reported and where possible, we calculated relative risks (RR) and 95 percent confidence intervals (CI).

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good," "fair," and "poor") using methods developed by the USPSTF, based on the number, quality, and size of studies; precision of estimates; consistency of results between studies; and directness of evidence.[45]

We conducted meta-analyses to calculate risk ratios for progression from IFG or IGT to DM and for effects of interventions using the DerSimonian–Laird random effects model with RevMan software (Review Manager Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). When statistical heterogeneity was present, we performed sensitivity analysis using the profile likelihood method using Stata (Stata 10.1), as the DerSimonian–Laird model results in overly narrow confidence intervals in this situation.[46] We stratified results by drug class or lifestyle intervention where appropriate. Statistical heterogeneity was assessed using the I^2 statistic.[47] We performed additional sensitivity analyses based on study quality and presence of outlier trials.

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and Federal and non-Federal collaborative partners.

Chapter 3. Results

Contextual Question 1. What Is the Yield (Incidence) of Starting Screening at Different Ages or Rescreening at Different Intervals in Adults With an Initial Normal Fasting Blood Glucose, Hemoglobin A1c, or Glucose Tolerance Test?

The ADA recommends screening for DM in persons without known risk factors for DM starting at age 45 years.[16] This recommendation is based on the increased prevalence of DM after age 44 years (**Table 2**).[17] Based on NHANES data from 2005 to 2008, about 4 percent of the U.S. population ages 20 to 44 years had diagnosed or undiagnosed DM. Corresponding proportions in persons ages 45 to 64 years and age 65 years and older were 14 percent and 27 percent, respectively.[17] Over age 44 years, men generally have slightly higher prevalence than women; blacks have higher prevalence relative to whites (**Table 2**).

Evidence on the yield of rescreening remains limited. The prior USPSTF report[1] found one study on rescreening older adults with initially normal glucose levels.[48] It screened community-based, healthy volunteers over age 65 years (mean baseline age 72 years) with an initial fasting serum glucose less than 126 mg/dL annually. The study population was 97 percent white and described as "upper middle class." Ninety-six percent of study participants had at least six annual screens over a mean 12 years followup, over which time fasting serum glucose declined for most participants. Four participants developed DM during followup, none of whom were older than age 75 years at baseline.

Results from the Ely cohort,[49] a single-center RCT of screening conducted in the United Kingdom and published since the prior USPSTF report, provide some evidence on the yield of rescreening. In this study, mean age was 50 years, about half of study participants were women and risk factors were not assessed prior to screening. Participants (n=1,106) who had initial negative screening results were rescreened 5 years and 10 years later; the corresponding yield of screening was 2 percent and 3 percent for DM.

A large (n=16,313) retrospective cohort study of middle-aged (median age 50 years) Japanese reported the yield of annual screening for three consecutive years in patients without DM at baseline.[50] In 14,800 participants, the overall yield of rescreening for DM with HbA1c was 3.2 percent. Incidence was highest in those with baseline HbA1c levels ranging from 6.0 to 6.4 percent (20% [95% CI, 18% to 23%]). Fewer participants with slightly lower HbA1c at baseline progressed to DM (baseline 5.5% to 5.9%: cumulative incidence 1.2% [95% CI, 0.9% to 1.6%]) and nearly all of those with HbA1c less than 5.5 percent at baseline did not develop DM (cumulative incidence 0.5% [95% CI, 0.001% to 0.3%]). This study may have limited applicability to U.S. settings due to differences related to the Japanese setting and population. For example, mean BMI at baseline was 22.5 kg/m^2, much lower than the U.S. average of 28 kg/m^2 to 29 kg/m^2 in a similarly aged population.[51]

A 2010 modeling study of DM screening strategies found that beginning screening at age 30

years with rescreening every 3 years or beginning screening at age 45 years with annual rescreening would result in a similar DM diagnosis lead-time of about 6 years (see Contextual Question 3 for more detailed discussion of modeling studies).[52]

Contextual Question 2. What Is the Utility of Using Formal Risk Calculators Versus Risk Factors (e.g., Family History, Body Mass Index) in Determining a Person's Risk For Developing Diabetes?

Several risk models or scores have been developed to assist clinical decisionmaking concerning screening for DM.[53] "Basic" risk models use information from patient history or medical records, including variables such as age, race, and family history, without requiring laboratory testing, and "extended" risk models also include results of blood tests (e.g., lipid profile, fasting glucose).

A systematic review of 94 risk models in populations not preselected on the basis of known risk factors for DM (n=399 to 2.54 million), reported areas under the receiver operating characteristic (AUROC) curve of 0.60 to 0.91 for incident DM during 3 years to 28 years of followup (DM incidence ranged from 1% to 21% in the studies).[53] The systematic review identified seven risk prediction tools with potential for use in routine clinical practice with AUROCs that ranged from 0.72 to 0.85 (**Table 3**).[53] These tools utilized similar components, most commonly age, BMI/obesity, blood pressure or use of antihypertensive medications, and family history of DM. Four (Ausdrisk, FINDRISC, QDScore, and the Cambridge Risk Score) did not measure fasting glucose as a risk factor in their scoring and are more applicable for guiding initial screening decisions. The discriminatory performance of individual risk factors was not assessed.

Another systematic review that included 46 prospective cohort studies of risk prediction models reported AUROCs for prediction of incident DM that ranged from 0.7 to 0.8 for "basic" models and 0.68 to 0.85 for "extended" models.[54] Both reviews found that models that incorporated novel biomarkers such as genetic information did not demonstrate improved discriminatory performance compared with those without such information.[53,54]

Evidence on the comparative performance of different risk models in a specific population is limited. A study that compared three DM risk prediction scoring models in a multiethnic U.S. cohort (n=5,329) reported the discriminative value of risk models derived from the Framingham Offspring, Atherosclerosis Risk in Communities (ARIC), and San Antonio Heart Studies, as well as the discriminatory value of individual risk factors.[55] All models included fasting glucose—limiting their utility to guide initial screening—as well as high-density lipoprotein (HDL), blood pressure, and family history. In this study, diagnosis of incident DM was based on the first followup visit during which a participant self-reported use of oral hypoglycemic drugs or insulin or had a fasting serum glucose greater than or equal to 126 mg/dL. At baseline, mean age was 62 years, 47 percent were male, and 43 percent were white. During a median of 5 years of followup, 446 incident cases of DM were diagnosed (9% of the population). All models were associated with similar discrimination (c-statistic ranged from 0.78 and 0.84). The Framingham and ARIC

models demonstrated similar discrimination for all racial groups, but the San Antonio model performed more poorly for black versus white participants ($p<0.05$). Individual risk factors performed more poorly than the prediction models (c-statistics ranging from 0.59 to 0.74; $p<0.01$ vs. models). In terms of calibration, the Framingham risk model underestimated risk of DM, the San Antonio model overestimated risk, and the ARIC model was accurate in all except the highest risk quintile. When models were recalibrated using mean DM incidence rates and risk estimates from the current study's cohort, all the prediction models showed good calibration (Hosmer–Lemeshow goodness-of-fit test; $p>0.10$).[55]

A study that evaluated the performance of 25 prediction models (12 basic and 13 extended) in a large (n=38,379) Dutch cohort, reported an AUROC ranging from 0.74 to 0.84 for basic models and 0.81 to 0.93 for extended models for risk of DM at 7.5 years (2.2 incident cases of DM per 1,000 person-years).[56] Most models overestimated the predicted risk of DM. Recalibration based on the incidence of DM in the studied cohort improved model performance.

Contextual Question 3. What Is the Utility of Existing Modeling Studies of Type 2 Diabetes Screening Versus No Screening in Examining Important Health Outcomes?

The prior USPSTF report[1] included seven modeling studies on screening.[57-63] This included two more recent high-quality studies that found targeted screening for DM in persons with hypertension relatively cost-effective when macrovascular benefits of optimal blood pressure control were considered.[57,62] These models also found that older persons benefitted more from screening than younger persons.[57,62] For example, population-based screening with HbA1c, assuming 50 percent uptake of screening and lifetime followup, was estimated to have an incremental cost-effectiveness ratio (ICER) of £2,266/quality-adjusted life-year (QALY) in persons ages 40 to 70 years versus no screening. When stratified by age, the ICER was much higher in the youngest group (ages 40 to 49 years: £10,216/QALY) than in the oldest group (ages 60 to 69 years: £1,152/QALY). The same study estimated ICERs of £1,505/QALY in persons with hypertension and £1,046/QALY in obese persons.[57] These findings were sensitive to assumptions regarding the degree of blood glucose control, future treatment protocols, and cost of statins.

We identified four modeling studies published since the prior USPSTF report on the cost-effectiveness of various screening strategies for DM, IFG, or IGT versus no screening in the United States, United Kingdom, or Canada (**Table 4**).[52,64-66] All were performed prior to the publication of the large ADDITION (Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) trial on DM screening in a higher-risk population, which found no differences after 10 years between persons who were screened and not screened in risk of all-cause, cardiovascular, or DM-related mortality (see Key Question 1)[67] or between intensive versus less intensive treatment in screen-detected persons with DM after 5 years of followup (see Key Question 5).[68,69] The modeling studies all included assumptions regarding benefits in patients with screen-detected DM from subsequent treatments and reduced progression of disease. These assumptions were primarily based on results of the Diabetes Prevention Program (DPP), which evaluated effects of pharmacological and lifestyle

interventions on DM progression, in conjunction with the modeled natural history of DM and associated clinical outcomes. All of the studies found screening versus no screening to be associated with ICERs of under $15,000/QALY, well under traditional thresholds for cost-effectiveness, in scenarios in which screening began at ages 40 or 45 years. Screening tests, when described, were based on capillary blood glucose, fasting plasma glucose, and OGTT, with no study evaluating HbA1c as the screening strategy. However, conclusions were generally insensitive to costs and other assumptions related to the screening test used. Three of the studies evaluated screening strategies that included treatment of DM, IFG, or IGT, and the fourth[52] only included screening and treatment of DM. In the ADDITION trial, screening focused on identification of DM, but clinicians were informed of screening results, specific therapies were not dictated, and the proportion of patients who were diagnosed with or received treatment for IFG or IGT was not reported.

No study reported the timeframe over which incremental benefits were observed with regard to time since screening. One study that included screening and management of IFG or IGT found screening to be cost-effective when modeled to a horizon of 10 years.[66] Another study found that cost-effectiveness was not observed for at least 30 years after screening.[64] Information about the timing of accrued benefits would be helpful for evaluating the consistency of model results with findings from the ADDITION trial, in which no benefits were observed within 10 years of screening.

Similar to the ADDITION trial, one of the modeling studies evaluated one-time screening.[64] The other studies evaluated strategies that included rescreening. All of the models appeared to assume complete attendance with screening. In the ADDITION trial, 78 percent of those invited to screening participated, and primary analyses were based on invitation to screen.

One of the United States studies was based on the Archimedes model, focused on screening and treatment for DM, and used a 50-year time horizon.[52] A strength of the Archimedes model is that assumptions regarding rates of DM progression and associated outcomes have been well-validated against epidemiological and clinical studies, showing good calibration.[70] In this study, beginning screening with fasting plasma glucose at age 45 years followed by rescreening every 3 years was associated with an ICER of $9,731/QALY versus no screening, beginning at age 30 years and rescreening every 3 years with $10,512/QALY, and annual screening beginning at age 45 years with $15,509/QALY.[52] Less cost-effective strategies were waiting to start screening until age 60 ($25,738/QALY) or beginning at age 30 years and screening every 6 months ($40,778/QALY). Screening persons with hypertension was the most cost-effective strategy ($6,287/QALY to $6,490/QALY). Results were sensitive to the disutility assigned to the state of having DM diagnosed with or without symptoms. The expected number of events prevented by each screening strategy compared with no screening after 50 years of followup per 1,000 persons screened was 2 to 5 events for death, 3 to 9 events for MI, 3 to 9 events for microvascular complications, and 0 events to 1 event for stroke.[52] The strategies that involved screening persons with hypertension resulted in the highest estimates of number of events prevented for each outcome.

Other modeling studies evaluated strategies that included screening and subsequent treatments for IFG or IGT. Details regarding calibration of these models against epidemiological and

clinical studies were limited. A U.S. study based on a Markov model found screening for IFG or IGT (random capillary blood glucose followed by fasting plasma glucose or OGTT) followed by lifestyle interventions associated with ICERs of $8,181/QALY to $9,511/QALY versus no screening, over a lifetime horizon.[65] Findings were sensitive to assumptions regarding the effectiveness and costs of the lifestyle intervention, which was based on the DPP study. Modeling studies from the United Kingdom and Canada were generally consistent with the U.S. studies. A 2008 U.K. modeling study of screening for DM (without treatment for patients with IGT), screening for DM or IGT followed by lifestyle interventions, and screening for DM or IGT followed by pharmacological interventions in a population at above average risk reported ICERs of $27,860, $12,290, or $13,828, respectively, versus no screening, based on a 50-year time horizon.[64] A 2012 Canadian modeling study found that screening for DM, IFG, or IGT every 1, 3 or 5 years starting at age 40 (with annual screening in persons with IFG or IGT) dominated the nonscreening strategy (lower costs and more QALYs) over a 10-year horizon. For the three strategies, the cost/QALY were $2,367, $2,281, and $2,116 versus $2,890 with the nonscreening strategy.[66]

Contextual Question 4. Is There Evidence That Intensive Blood Pressure, Lipid Lowering, or Use of Aspirin Is More Effective in Persons With Diabetes Compared With Persons Without Diabetes?

Effects of more intensive blood pressure therapy, lipid lowering therapy, and use of aspirin in persons with DM is addressed in Key Question 5. This Contextual Question focuses on differences in effectiveness of these interventions in persons with versus without DM.

The 2008 USPSTF report[1] included evidence on the effect of more versus less intensive blood pressure lowering in persons with and without DM from a meta-analysis of five trials;[71] four trials[72-76] were older studies included in the 2003 USPSTF diabetes report[77] and the remaining study[78] enrolled only persons with kidney disease and without DM, and therefore was not included in older (pre-2008) USPSTF reports. Only the Hypertension Optimal Treatment (HOT) study[73] enrolled both persons with and without DM and stratified results according to DM status; the other studies enrolled patients with DM (with or without hypertension).[72,74-76] Target diastolic blood pressure (DBP) in the studies ranged from either less than or equal to 75 mm Hg to 85 mm Hg, or 10 mm Hg lower than DBP at baseline in the intensive groups and less than or equal to 80 mm Hg to 105 mm Hg in the standard treatment groups[72-75]; one study used mean arterial pressure targets of 92 mm Hg in the intensive group and 102 mm Hg to 107 mm Hg in the standard group.[78] Treatment regimens varied. In the intensive groups, angiotensin converting–enzyme (ACE) inhibitors, calcium channel blockers, and/or beta blockers were used in all of the studies. The standard treatment groups received placebo or no intervention in two studies,[73,78] and prohibited use of an ACE inhibitor, beta blocker, or calcium channel blocker in the three other studies.[72,74,75] In the five studies that contributed data to the meta-analysis, mean achieved blood pressures were 139/81 mm Hg in the intensive groups and 143/84 mm Hg in the standard treatment groups, or higher than in the more recent Action to Control Cardiovascular Risk in Diabetes (ACCORD)[79] and Action in Diabetes and Vascular Disease: Preterax and Diamicron

Modified Release Controlled Evaluation (ADVANCE)[80] trials of intensive antihypertensive therapy in persons with diabetes, in which mean achieved blood pressures were 119/64 mm Hg and 136/73 mm Hg with intensive therapy and 134/71 mm Hg and 140/73 mm Hg with standard therapy, respectively (see Key Question 5).

The largest study included in the meta-analysis was the HOT trial, which enrolled 1,501 persons with DM and 17,289 persons without DM.[73] Study participants had a mean baseline blood pressure of 170/105 mm Hg. All were treated with felodipine with the addition of dose-titrated ACE inhibitors, beta blockers, and/or diuretics necessary to achieve blood pressure targets. Patients were randomized to treatment goals of DBP less than or equal to 80 mm Hg (intensive lowering) versus less than or equal to 85 mm Hg or 90 mm Hg (combined as standard lowering because outcomes were very similar). Mean achieved blood pressure was 140/81 mm Hg in the intensive group and 143/84 mm Hg in the standard group. Results from the HOT trial and the overall results of the 2005 meta-analysis included in the prior USPSTF report are shown in **Table 5**. In HOT, intensive BP lowering in patients with DM was associated with decreased risk of all-cause mortality (RR 0.58 [95% CI, 0.34 to 0.98]) and CV mortality (RR 0.33 [95% CI, 0.15 to 0.74]), but not in patients without DM (RR 1.18 [95% CI, 0.99 to1.40] and RR 1.32 [95% CI, 1.01 to 1.72], respectively). Effects on cardiovascular events in persons with DM was of borderline statistical significance (RR 0.67 [95% CI, 0.45 to 1.00\), with no effect in those without DM (RR 1.01 [95% CI, 0.87 to 1.18]). Intensive blood pressure lowering was not associated with decreased risk of stroke in persons either with or without DM. In the meta-analysis (including HOT), intensive blood pressure lowering in persons with DM was associated with decreased risk of all-cause mortality (RR 0.73 [95% CI, 0.56 to 0.95]), CV mortality (RR 0.67 [95% CI, 0.40 to 1.12]), stroke (RR 0.64 [95% CI, 0.46 to 0.89]), and CV events (RR 0.75 [95% CI, 0.61 to 0.94]). For those without DM, intensive blood pressure lowering was associated with increased risk of CV mortality (RR 1.30 [95% CI, 1.01 to 1.66]) and had no effect on other outcomes.

The Felodipine Event Reduction (FEVER)[81] trial, published since the prior USPSTF report, on effects of more intensive blood pressure lowering[81] reported results stratified by DM status. This RCT, conducted in China, enrolled 9,711 patients with hypertension, including 1,241 persons with DM, to more intensive treatment with a calcium channel blocker and diuretic (felodipine plus hydrochlorothiazide) or standard treatment with a diuretic (hydrochlorothiazide) and placebo.[81] In the FEVER trial, achieved systolic blood pressure (SBP) was similar to the studies described above, with little separation between groups (138 mm Hg with combination therapy versus 142 mm Hg with diuretic monotherapy). Intensive blood pressure lowering treatment was associated with no reduction in risk of all-cause mortality (RR 1.00 [95% CI, 0.56 to 1.77]) or cardiovascular mortality (RR 1.01 [95% CI, 0.51 to 1.99]) in persons with DM, but was associated with decreased risk in persons with no DM (RR 0.64 [95% CI, 0.48 to 0.84] and RR 0.64 [95% CI, 0.45 to 0.92], respectively).[81] More intensive blood pressure therapy was associated with reduced risk of stroke in both persons with diabetes (RR 0.56 [95% CI, 0.34 to 0.92]) and without diabetes (RR 0.77 [95% CI, 0.62 to 0.96]). Possible explanations for the conflicting findings between this study and those in the earlier meta-analysis include the shorter duration of followup (mean 3 years versus 4 years to 8 years), lower achieved blood pressures, failure to achieve separation in blood pressure rates between more intensive and standard treatments, the specific antihypertensive therapies evaluated, or differences over time in the

management of patients with DM.

The prior USPSTF report did not evaluate effects of more versus less intensive lipid-lowering therapy in persons with DM versus without DM, though it determined that lipid-lowering therapy in general appeared to be similarly effective regardless of DM status.[1] This conclusion was primarily based on a meta-analysis that included six studies that found lipid-lowering therapy associated with similarly reduced risk of cardiovascular events in persons with DM (RR 0.79 [95% CI, 0.70 to 0.89]) and without DM (RR 0.77 [95% CI, 0.67 to 0.88]), relative to placebo.[82] These results were consistent with a more recent meta-analysis of 14 trials of statins, published since the prior USPSTF report, which found no difference in risk of vascular events in persons with DM (RR 0.79 [95% CI, 0.72 to 0.87]) or without DM (RR 0.79 [95% CI, 0.76 to 0.82]).[83] In the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, also published since the prior USPSTF report, persons with dyslipidemia were randomized to diet plus pravastatin or diet plus placebo.[84] The study enrolled 7,892 Japanese with DM (n=1,746), IFG (n=464), or normal glucose levels (n=5,622). Estimates for risk of all-cause mortality, stroke, coronary heart disease, and cardiovascular disease were very similar for the DM, IFG, and normal glucose groups (**Appendix B10**).

Prior USPSTF reports[1,77] included an older meta-analysis that found aspirin associated with no clear effect on risk of cardiovascular events in persons with DM (RR 0.93 [95% CI, 0.83 to 1.07]; see Key Question 5).[85] Using data from this meta-analysis, we calculated a pooled RR of 0.81 (95% CI, 0.78 to 0.83) in persons without DM. Results from two other studies included in the prior report,[1] the Primary Prevention Study[86] and the Women's Health Study,[87] also found no benefit with aspirin use in persons with DM compared with those without DM for vascular events[86] and stroke.[87] We did not identify any new studies on differential effects of aspirin use versus nonuse in persons with and without DM. The USPSTF is currently in the process of updating its recommendation on aspirin for primary prevention of cardiovascular events[88]; persons with DM are included as a subgroup in this review.

Key Question 1. Is There Direct Evidence That Systematic Screening (Either Targeted or Universal) For Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance in Asymptomatic Adults Improves Health Outcomes?

Summary

The previous USPSTF report found no RCTs on the effects of screening for DM on clinical outcomes.[1] One case control study (303 cases) found no association between screening and improvement in microvascular complications. We identified two RCTs on screening for DM versus no screening published since the prior report: the ADDITION-Cambridge trial (n=19,226)[67] and a study conducted in Ely, United Kingdom (n=4,936).[49,89] Both trials found no difference between invitation to screening and no invitation to screening in risk of all-cause mortality after approximately 10 years (HR 1.06 [95% CI, 0.90 to 1.25] and HR 0.79 [95% CI, 0.63 to 1.00], respectively).

Evidence

The good-quality ADDITION-Cambridge trial (n=19,226)[67] and the fair-quality Ely trial (n=4,936)[49,89] reported the effects of screening for DM on health outcomes (**Appendix B1 and B2; Table 6**). The ADDITION-Cambridge trial is part of the larger ADDITION-Europe trial, an ongoing trial on effects of screening for DM as well as effects of intensive versus standard treatment for screen-detected DM (see Key Question 5 for effects of treatment).[90] Both ADDITION-Cambridge and the Ely study were conducted in the United Kingdom. Mean age of study participants ranged from 51 years to 58 years, 36 percent to 54 percent were women, and followup was 10 years.[49,67,89] Methodological shortcomings in the Ely study included inadequate detail regarding methods of randomization, unclear allocation concealment, and baseline differences between groups (**Appendix B1**).[49]

Both studies were conducted in general practices, though they used different methods to identify participants. In ADDITION-Cambridge, persons at high-risk for DM (based on known risk factors) were cluster-randomized by general practice site to screening (n=16,047 participants from 27 practice sites; of 16,047 randomized participants, 15,089 [94%] were invited to screening) or no screening (n=4,137 participants from five practice sites).[67] The Ely study randomly enrolled participants to screening (n=1,705) or no screening (n=3,231) from a single practice site without consideration of baseline risk of DM (study phase 1).[49] Screening for DM was performed with initial random capillary blood glucose and HbA1c, followed by confirmatory OGTT in the ADDITION-Cambridge study, while the Ely study used OGTT for initial screening. ADDITION participants underwent one-time screening, while Ely participants in the screening groups were invited back for subsequent screenings after 5 years and 10 years. Seventy-eight percent (11,737/15,089) of those invited to screening underwent screening in the ADDITION trial,[67] while participation in the Ely study was slightly lower (1,157/1,705; 68%).[49] Factors associated with attendance at screening were older age and prescription of antihypertensive medication, female sex, and lower BMI in the ADDITION study,[67] and those attending screening in the Ely study were less socioeconomically disadvantaged, with younger persons and women more likely to attend in some screening cycles.[49] To obtain a sufficient number of persons with screen-detected DM, 22 additional screening sites were added in the ADDITION study, with no additional nonscreening sites.[67] Prevalence of DM at the time of initial screening was 3 percent in both the ADDITION-Cambridge and the Ely study.

There was no significant difference between screening and no screening in risk of all-cause mortality in both the ADDITION (HR 1.06 [95% CI, 0.90 to 1.25])[67] and Ely (unadjusted HR 0.96 [95% CI, 0.77 to 1.20]; adjusted HR 0.79 [95% CI, 0.63 to 1.00])[67] studies (**Table 6**). In ADDITION-Cambridge, those who were invited to screening but did not attend had a higher risk of all-cause mortality compared with those who were invited to and attended screening (HR 2.01, [95% CI, 1.74 to 2.32]). In the Ely study, those who were invited but did not attend screening had increased risk of mortality versus those who were not invited to screening (unadjusted HR 1.68 [95% CI, 1.27 to 2.22]; adjusted HR 1.36 [95% CI, 1.01 to 1.82]; **Table 6**).

Ten years after study initiation, a subset of never-screened Ely participants were randomized to invitation to screening (n=1,577) or no screening (n=1,425; study phase 2). After 8 years followup, there was no difference in all-cause mortality between invitation to screening and no

screening (unadjusted HR 1.20 [95% CI, 0.95 to 1.51]; adjusted HR 1.18 [95% CI, 0.93 to 1.51]; **Table 6**).[49] As with the results from phase 1 of the Ely studies, those who were invited but did not attend screening had increased risk of mortality versus the nonscreening group (unadjusted HR 1.85 [95% CI, 1.45 to 2.36]; adjusted HR 1.73 [95% CI, 1.34 to 2.24]).

There was also no difference in the ADDITION trial between screening and no screening in risk of cardiovascular mortality (HR 1.02 [95% CI, 0.75 to 1.38]), cancer-related mortality (HR 1.08 [95% CI, 0.90 to 1.30]), DM-related mortality (HR 1.26 [95% CI, 0.75 to 2.10]), or death due to other causes (HR 1.10 [95% CI, 0.87 to 1.39]; **Table 6**).[67] Nonmortality health outcomes were not reported in either study.

Of the original 4,936 patients enrolled in phase 1 of the Ely study, 152 persons with DM (92 from the screening group; 60 from the nonscreening group) underwent additional assessment after 12 years followup.[89] Diagnosis of DM occurred 3.3 years earlier in the screening group compared to the nonscreening group (diagnosis 5.0 years vs. 1.7 years prior, p=0.006). Despite the observed lead time with screening, there was no difference in health outcomes between screening and no screening (**Table 6**).

Key Question 2. What Are the Harms of Screening Adults for Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance?

Summary

The previous USPSTF report found limited evidence on the harms of screening for DM, IFG, or IGT, and no studies reported serious psychological or other adverse effects associated with a new diagnosis of DM.[1] We identified three studies published since the prior report on psychological effects associated with screening or a new diagnosis of DM. Although one study found invitation to screening for DM and a new diagnosis of DM associated with short-term anxiety,[91] two longer-term studies found no negative psychological effects associated with invitation to screening or notification of positive DM status.[92, 93]

Evidence

The previous USPSTF report found limited evidence on the harms of screening for DM, IFG, IGT.[1] No study reported serious psychological or other adverse effects associated with a new diagnosis of DM. The ADDITION-Cambridge study[94] found that subjects who screened positive for DM reported poorer health, higher anxiety, more depression, and more DM-specific worry than those with a negative screening test at the time of screening.

We identified three studies published since the prior USPSTF report on psychological effects of screening or a new diagnosis of DM (**Appendix B1 and B2**). A fair-quality pilot study for the ADDITION trial randomized 355 patients at high risk for DM.[91] Participants who were invited to and attended screening and who had completed a self-rated psychological assessment (n=77/116;

66%) reported higher scores for anxiety based on the short form Spielberger State Anxiety Inventory (scale 20 to 80, higher score indicates greater anxiety; mean score 37.6) compared with those not invited to screening (mean score 34.1; p=0.015), measured 6 weeks to 14 weeks after last contact with study personnel. In those screened, the six participants who were diagnosed with DM reported higher mean anxiety scores versus those screened and found to not have DM (46.7 vs. 37.0, p=0.031). There was no difference between the invited and not invited groups on a single-item, 5-point Likert scale on self-perceived health (invited score 2.97 vs. not invited score 2.95; p=0.82) and on illness representation subscales.[91]

A followup study of the Ely cohort found no differences between persons initially screened and found to be without DM (n=731) versus those unscreened (n=1694) in self-reported use of antidepressant or anxiolytic medications (p=0.4 and 0.8, respectively), physical and mental health summary scores on the SF-36 or the EuroQol-5D score after 13 years.[92] Similarly, a subgroup analysis of screened ADDITION-Cambridge (n=3,240) participants found no differences between those informed that they did or did not have DM in measures of anxiety or depression (as measured by the Hospital Anxiety and Depression Scale) at 12 months followup (p-values not reported).[93]

We identified no studies on psychological effects associated with a diagnosis of IFG or IGT. We also identified no studies on harms associated with false positive tests for DM, IFG, or IGT.

Key Question 3. Do Interventions for Screen-Detected or Early Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance Provide an Incremental Benefit in Health Outcomes Compared With No Interventions or Initiating Interventions After Clinical Diagnosis?

Summary

The prior USPSTF report identified no trials on the effects of interventions for screen-detected DM on health outcomes, and limited evidence from five trials of persons with IFG or IGT showed no clear effect on all-cause or cardiovascular mortality or other health outcomes.[1] New evidence from 12 trials (in 14 publications) found that lifestyle modification or early use of pharmacologic interventions for glycemic control or blood pressure therapy did not reduce risk of all-cause mortality, cardiovascular mortality, or stroke, but most trials were underpowered to evaluate these outcomes.[95-109] One study of lifestyle modification found a reduction in all-cause and cardiovascular mortality after 23 years followup.[110] Lifestyle modification, but not metformin, was associated with better quality of life based on physical health scores in a fair-quality trial (n=3,234).[100]

Evidence

The prior USPSTF report included one good-quality trial and four fair-quality trials that found no

clear evidence that interventions improve health outcomes in persons with screen-detected or early DM, IFG, or IGT. We identified 13 studies (in 16 publications) published since the prior report on effects of interventions on health outcomes in these populations (**Appendix B3**),[95-110] including longer followup or new analyses from three studies included in the prior report.[99,100,108] Studies evaluated the effect of glucose-lowering agents (six studies)[98,101,103,105,106,109] antihypertensive agents (two studies)[99,104] and lifestyle modification (five studies in seven publications)[95-97,100,102,108,110] compared with placebo or usual care. No study enrolled a screen-detected DM population. Two studies[95-97] enrolled persons with early DM, and the remainder enrolled those with IFG or IGT. Mean age ranged from 45 to 64 years, and 13 percent to 69 percent of the population in these studies were women. Duration of followup ranged from 1 year to 23 years (median 3 years). Six studies were rated good-quality and five were rated as fair-quality; no studies were poor-quality (**Appendix B4**). Limitations of the fair-quality studies were unclear methods of randomization and allocation concealment and lack of details regarding blinding.

The effect of interventions on progression to DM in patients with IFG or IGT is discussed in Key Question 6.

All-Cause and Cardiovascular Mortality

Studies of glucose-lowering interventions included in the previous USPSTF report found no difference in risk of all-cause or cardiovascular mortality with rosiglitazone,[15] metformin,[7,13] or acarbose[111] versus placebo in persons with IFG or IGT, though event rates were very low (≤1%) in all groups.

Five studies published since the prior USPSTF report evaluated risk of all-cause mortality with acarbose,[105] voglibose,[101] pioglitazone,[98,106] or nateglinide[103] versus placebo for IFG or IGT (**Table 7; Appendix B3**). No individual trial reported a beneficial effect on mortality. A pooled analysis of these five trials plus the three trials included in the prior USPSTF report also found no reduction in all-cause mortality after 3 years to 5 years followup (RR 1.00 [95% CI, 0.87 to 1.16]; I^2=0%; **Figure 2**).[7,98,99,101,103,105,106,111] Stratified analyses based on drug class did not affect the findings. Pharmacological therapies for IFG or IGT also were associated with no reduction in cardiovascular mortality (RR 1.07 [95% CI, 0.84 to 1.35], I^2=0%; **Figure 3),** based on pooled results from three trials included in the previous report (one each of acarbose,[112] metformin,[13] and rosiglitazone[15]) plus two trials published since the prior report (one each of pioglitazone[106] and nateglinide[103]). The pooled estimates for all-cause and cardiovascular mortality were both dominated by the large (n=9,306) NAVIGATOR study.[103]

Trials of antihypertensive medication for IFG or IGT also found no reduction in all-cause or cardiovascular mortality with ramipril (HR 0.98 [95% CI, 0.60 to 1.61] and HR 1.21 [95% CI, 0.52 to 2.80])[14,99] or valsartan (HR 0.90 [95% CI, 0.77 to 1.05] and HR 1.09 [95% CI, 0.85 to 1.40])[104] versus placebo after 3 years and 7 years, respectively, in persons with IFG or IGT (**Table 7; Appendix B3**).

Three studies of lifestyle modification interventions versus usual care included in the prior report and one study published since the prior report found no difference in all-cause mortality between

groups after 1 year to 3 years followup in persons with early DM, IFG, IGT, though they were underpowered to evaluate this outcome.[6,7,13,95] There remained no difference in all-cause mortality after 10 years followup in the Finnish Diabetes Prevention Study (DPS) in persons receiving intensive diet and exercise counseling versus a control group given general health behavior information (HR 0.57 [95% CI, 0.21 to 1.58]; **Appendix B3**).[108]

Results were similar in another study of lifestyle modification (either diet or exercise alone, or diet plus exercise) versus general DM or IGT health information in risk of all-cause and cardiovascular mortality after 20 years followup (HR 0.96 [95% CI, 0.65 to 1.14] and HR 0.83 [95% CI, 0.48 to 1.40], respectively).[102] However, after 23 years followup, both all-cause mortality (HR 0.71 [95% CI, 0.51 to 0.99]) and cardiovascular mortality (HR 0.59 [95% CI, 0.36 to 0.96]) were significantly reduced in the lifestyle modification group (**Table 7**).[110] Limitations of the study include a relatively small sample size (n=577; 439 in the intervention group and 138 in the control group). Also, mortality was not a prespecified outcome and study participants were not regularly monitored beyond the 6-year intervention (deaths were ascertained using hospital records and physician interviews). Additionally, the study was conducted in China, which may limit applicability to a U.S. population.

Cardiovascular Events

One fair-quality trial included in the prior report found acarbose for IGT associated with reduced risk of acute MI (HR 0.09 [95% CI, 0.01 to 0.72]) and total cardiovascular events (including MI, new angina, revascularization, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease; HR 0.51 [95% CI, 0.28 to 0.95]) versus placebo.[112] However, three additional good-quality trials of nateglinide, [103] rosiglitazone with[109] or without[99] metformin, and one fair-quality trial or pioglitazone[98] published since the prior USPSTF report found no beneficial effect on risk of MI versus placebo when patients were followed for 2 years to 5 years (**Table 7**; **Appendix B3**).

Two studies of antihypertensive medications in patients with IFG or IGT found no reduction in risk of MI with ramipril (HR 1.29 [95% CI, 0.59 to 2.84])[99] or valsartan (HR 0.97 [95% CI, 0.77 to 1.23])[104] versus placebo after 3 years and 5 years follow-up, respectively. Risk estimates for heart failure were imprecise or showed no effect (HR 3.06 [95% CI, 0.99 to 9.48] for ramipril; HR 0.97 [95% CI, 0.72 to 1.29] for valsartan; **Table 7** and **Appendix B3**).

Two trials[7,13] included in the prior USPSTF report found no difference in cardiovascular events or cardiovascular morbidity with lifestyle modification versus usual care in patients with IGT or IFG.[1] These results were consistent with 10 years followup and 20 years followup in the Finnish DPS[108] and the Da Qing[102] studies (two fair-quality studies of diet, exercise, or diet plus exercise and physical activity, weight reduction, and dietary counseling, respectively, published since the prior report), though event rates were low in both studies (**Table 7**; **Appendix B3**).

Stroke

A fair-quality study included in the prior USPSTF report found no difference in risk of stroke with acarbose versus placebo (HR 0.56 [95% CI, 0.10 to 18.30]).[112] and two studies published

since the prior USPSTF report, found that no association between rosiglitazone (HR 1.40 [95% CI, 0.44 to 4.40][99]) or nateglinide (HR 0.89 [95% CI, 0.69 to 1.15])[103] versus placebo in risk of stroke after 3 years and 5 years, respectively. Trials of the antihypertensive medications ramipril (HR 0.50 [95% CI, 0.15 to 1.66])[99] and valsartan (HR 0.79 [95% CI, 0.61 to 1.02])[104] also showed no effects on risk of stroke versus placebo in persons with IFG or IGT after 5 years (**Table 7**; **Appendix B3**).

Renal Disease

No studies reported incidence of serious renal disease as an individual outcome. The DREAM trial reported a composite renal outcome that included intermediate (e.g., progression from normal albuminuria to microalbuminuria) and clinical (renal insufficiency requiring dialysis or transplantation) outcomes. It found rosiglitazone (HR 0.80 [95% CI, 0.68 to 0.93]) but not ramipril (HR 0.97 [95% CI, 0.83 to 1.14]) associated with reduced risk versus placebo after 3 years (**Table 7**; **Appendix B3**).[99]

Quality of Life

Two studies reported quality of life measures. Followup from the Diabetes Prevention Program study (n=3,234)[100] found an intensive lifestyle intervention associated with better SF-36 scores for general health (+3.2, p<0.01), physical function (+3.6, p<0.01), bodily pain (+1.9, p<0.01), and vitality (+2.1, p<0.01) versus placebo (**Appendix B3**). In the same study, there was no difference between metformin and placebo on quality of life measures. A second study that compared a single education session plus usual care with usual care and no education component in persons with newly diagnosed diabetes found no difference in quality of life measures at 1 year followup[96] and 3 years followup. [97]

Key Question 4. What Are the Harms of Interventions for Screen-Detected or Early Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance?

Summary

The previous USPSTF report[1] found no studies that reported serious harms and no studies of harms associated with interventions in persons with screen-detected DM. Most studies conducted in persons with IFG or IGT included in the 2008 USPSTF report found no differences in withdrawal rates between lifestyle or pharmacologic interventions and placebo or usual care.

Studies of interventions for screen-detected or early DM, IFG, or IGT published since the 2008 USPSTF report found few differences between lifestyle or pharmacologic interventions versus usual care or placebo in risk of harms, though evidence was limited. One trial found acarbose associated with higher risk of withdrawal due to adverse events versus placebo.[105] Rosiglitazone was associated with increased congestive heart failure in one trial, though the estimate was imprecise (HR 7.04 [95% CI, 1.60 to 31]).[99] There was also no difference in risk of serious

adverse events between interventions and placebo or usual care in three other studies,[101,106,107] but few events were reported. A large, good-quality study found nateglinide associated with increased risk of hypoglycemia versus placebo (20% vs. 11%; RR 1.73 [95% CI, 1.57 to 1.92]) and valsartan associated with increased risk of hypotension-related adverse events (42% vs. 36%; RR 1.16 [95% CI, 1.11 to 1.23]).[103,104]

Evidence

The previous USPSTF report[1] found no studies of harms associated with interventions for screen-detected DM. Most studies conducted in persons with IFG or IGT included in the 2008 USPSTF report found no differences in withdrawal rates between lifestyle or pharmacologic interventions versus control placebo or usual care,[4,6,113] though one study reported a higher risk of withdrawal with acarbose versus placebo (RR 1.63 [95% CI, 1.34 to 1.97]).[111] For treatment of DM in general (not restricted to screen-detected cases), systematic reviews included in the 2008 USPSTF report found hypoglycemia more common with sulfonylureas versus other glucose-lowering drugs (e.g., metformin, TZDs) and with glyburide versus other secretagogues (RR 1.83 [95% CI, 1.21 to 1.92]) and other sulfonylureas (RR 1.83 [95% CI, 1.35 to 2.49]).[1]

We identified four good- and five fair-quality trials published since the 2008 USPSTF report that reported harms associated with interventions for screen-detected or early DM, IFG, or IGT (**Appendix B5**).[96-98,101,103-107,109] The fair-quality studies had unclear methods of randomization, allocation concealment, and/or blinding (**Appendix B4**). One study was conducted in persons with screen-detected or early DM, and the other seven enrolled persons with IFG or IGT. Two studies evaluated the effects of lifestyle interventions[96,97,107] and seven evaluated pharmacologic interventions, including TZDs (three studies),[98,106] alpha-glucosidase inhibitors (two studies),[101,105] nateglinide and valsartan (one study),[103,104] metformin (one study),[177] and combination therapy (one study).[109] Sample sizes ranged from 118 participants to greater than 9,000 participants, and duration of followup was from 1 to 5 years. No study was specifically designed to assess harms.

Withdrawals due to adverse events were reported in three studies of pharmacologic interventions published since the 2008 USPSTF report. Two of these studies reported no difference in risk of withdrawals between active intervention and placebo (**Appendix B5**).[101,103,104] In the other study, acarbose was associated with higher risk of withdrawal due to adverse events than placebo (37% vs. 14%; RR 2.66 [95% CI, 1.29 to 5.48]).[105] This finding was consistent with a study of acarbose versus placebo included in the prior USPSTF report (29% vs. 18%; RR 1.63 [95% CI, 1.34 to 1.97]).[111]

Two trials found pioglitazone (50% vs. 42%; RR 1.23 [95% CI, 1.03 to 1.47])[98] and voglibose (90% vs. 85%; RR 1.06 [95% CI, 1.02 to 1.10])[101] associated with increased risk of any adverse event versus placebo. In these trials, serious adverse events were rare, with no difference between voglibose (0.6% vs. 0.2%; RR 2.46 [95% CI, 0.48 to 13])[101] or pioglitazone (2% vs. 5%; RR 0.41 [95% CI, 0.13 to 1.29])[106] versus placebo. Rosiglitazone was associated with increased congestive heart failure (HR 7.04 [95% CI, 1.60 to 31]) in the DREAM trial, though this estimate was imprecise.[99] A placebo-controlled trial of acarbose included in the prior report[112] and three trials of pioglitazone,[98] nateglinide,[103] or metformin plus rosiglitazone[109]

published since the prior report found no new or worsening heart failure events, although few events were reported in three of these trials (**Appendix B3**).[98,109,112] One trial found nateglinide associated with increased risk of hypoglycemia versus placebo (20% vs. 11%; RR 1.73 [95% CI, 1.57 to 1.92]) and valsartan associated with increased risk of hypotension-related adverse events (42% vs. 36%; RR 1.16 [95% CI, 1.11 to 1.23]).[103,104] Two trials found no difference between pioglitazone[98] or metformin plus rosiglitazone[109] versus placebo in risk of cancer, though the trials were not designed to evaluate this outcome and were underpowered (**Appendix B5**). No trial of metformin reported risk of lactic acidosis, while one trial reported no differences in serious or not serious hypoglycemia or serious anemia.[177]

Two studies published since the prior report on educational lifestyle interventions versus usual care reported few adverse events, with no difference in risk of all-cause withdrawal rates in one study (5% vs. 6%; RR 0.81 [95% CI, 0.45 to 1.44)[96] and no serious adverse events in the other study (**Appendix B5)**.[107]

No observational study of harms associated with pharmacological interventions focused on populations with screen-detected or early DM.

Key Question 5. Is There Evidence That More Intensive Glucose, Blood Pressure, or Lipid Control Interventions Improve Health Outcomes in Adults With Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance Compared With Traditional Control? Is There Evidence That Aspirin Use Improves Health Outcomes in These Populations Compared With Nonuse?

Summary

The previous USPSTF report included no studies of more versus less intensive glucose, blood pressure, or lipid control for screen-detected DM.[1] For DM not specifically screen-detected, the prior report found intensive glycemic control associated with reduced risk of various composite vascular events, intensive blood pressure control associated with reduced cardiovascular morbidity, and no evidence on the effect intensive lipid control on health outcomes, versus standard therapy.[1] The prior USPSTF report also included a systematic review that found aspirin use in persons with DM associated with a small, nonstatistically significant benefit in reducing risk of cardiovascular events (RR 0.93 [95% CI, 0.83 to 1.07]).[85]

The ADDITION-Europe study of persons with newly screen-detected DM (baseline HbA1c 6.5%) published since the prior report found no difference between treatment with an intensive multifactorial intervention aimed at glucose, blood pressure, and lipid-lowering and standard treatment in risk of all-cause mortality (HR 0.91 [95% CI, 0.69 to 1.21]), cardiovascular mortality (HR 0.83 [95% CI, 0.65 to 1.05]), MI (HR 0.70 [95% CI, 0.41 to 1.21]), stroke (HR 0.98 [95% CI, 0.57 to 1.71]) or revascularization (HR 0.79 [95% CI, 0.53 to 1.18]) after 5

years.[68,69]

For DM not specifically identified by screening, many good-quality systematic reviews found fair to good-quality, consistent evidence that intensive glucose lowering to a target HbA1c of less than 6 percent to 7.5 percent was associated with no reduction in all-cause or cardiovascular mortality compared with less-intensive therapy.[114-124] Intensive glucose-lowering therapy was associated with reduced risk of nonfatal MI in six reviews (pooled RR range 0.83 to 0.87) and retinopathy in three reviews (pooled RR 0.75 to 0.80).[114,117,118,121,122,124]

Intensive BP lowering reduced risk of all-cause mortality and stoke in a good-quality systematic review[125] but large, recently published trials are inconsistent with respect to effects of more versus less intensive blood pressure therapy in patients with DM. The ADVANCE trial[80,126] found the addition of an ACE inhibitor plus diuretic associated with decreased risk of all-cause and cardiovascular mortality, and the ACCORD study[127,128] found no difference between a systolic blood pressure (SBP) target of 140 mm Hg versus 120 mm Hg in risk of all-cause or cardiovascular mortality. Limited evidence from two trials of persons with DM found no benefit from the addition of a fibrate to statin monotherapy or the addition of statin to lifestyle interventions in risk of all-cause or cardiovascular mortality.[84,129] Two trials found use of multifactorial interventions in persons with DM aimed at more intensive glucose, blood pressure, and/or lipid lowering associated with reduced risk of all-cause and cardiovascular mortality.[130,131] Two good-quality systematic reviews found fair-quality evidence of no effect of aspirin use versus nonuse on health outcomes in persons with DM, including all-cause mortality, cardiovascular mortality, MI, and stroke.[132,133]

Evidence

We identified 13 good-quality systematic reviews (**Appendix B6, B7, and B8**)[114-125,134] and 10 trials (in 33 publications; **Appendix B9, B10 and B11**)[68,69,79,80,84,126-131,135-156] published since the prior USPSTF report on the effects of more intensive glucose, blood pressure, or lipid control or the use of aspirin on health outcomes. This includes the primary publications of the treatment phase of the ADDITION trial (conducted in persons with screen-detected DM)[68,69] the large ACCORD[127,128] and ADVANCE trials,[80,126,145] and their many substudies. Four of the trials were rated fair-quality[68,69,84,148-151] and the remainder were rated good-quality. Common limitations of the fair-quality trials were unclear methods of randomization and treatment allocation (**Appendix B11**). Studies ranged in size from 160 participants to more than10,000 participants, with followup from 3 to 13 years; mean age was 53 to 72 years. Only the ADDITION trial enrolled a screen-detected DM population,[68,69,135-137] all other trials enrolled persons with DM not specifically screen-detected.

Screen-Detected Diabetes

The prior USPSTF report included no studies of more versus less intensive glucose, blood pressure, or lipid control for screen-detected DM.[1] The recently published fair-quality treatment phase of the ADDITION-Europe trial evaluated effects of more intensive treatment for screen-detected DM (**Appendix B9**).[68,69,138] Patients, but not caregivers, were blinded to treatment allocation. Study participants were residents of Denmark (n=1,533), United Kingdom, (n=1,026),

or the Netherlands (n=498) and newly diagnosed with DM through screening. Mean HbA1c was 6.5 percent, about one-fourth of participants were smokers, mean BMI was 31.5 kg/m^2 (meeting criteria for obesity), and 6 percent to 7 percent had a history of MI at time of enrollment. The study used a cluster-randomized design in which care centers were randomized to a multifactorial intervention that included use of intensive glucose, blood pressure (BP), and lipid-lowering targets (HbA1c <7.0%, BP <135/85 mm Hg, and total cholesterol ≤4.5 mmol/L to 5.0 mmol/L, respectively), plus a lifestyle education component (n=1,678) or standard targets according to local guidelines (n=1,379). In the intensive treatment group, selection of glucose, blood pressure, or lipid-lowering therapy was determined using a prespecified treatment algorithm, and aspirin could be added if deemed necessary by caregivers. Participants were followed for 5 years or until the first cardiovascular event (the primary outcome), which included cardiovascular mortality, nonfatal MI or stroke, revascularization or (nontraumatic) amputation (**Appendix B9**).[68]

There was no difference between groups in incidence of first cardiovascular event after adjustment for country (HR 0.83 [95% CI, 0.65 to 1.05]).[68] For specific outcomes, intensive treatment was also associated with no reduction in risk of all-cause mortality (HR 0.83 [95% CI, 0.65 to 1.05]) or cardiovascular mortality (HR 0.88 [95% CI, 0.51 to 1.51]), stroke (HR 0.98 [95% CI, 0.57 to 1.71]), MI (HR 0.70 [95% CI, 0.41 to 1.21]), or revascularization (HR 0.79 [95% CI, 0.52 to 1.18]; **Appendix B9**). Results for all-cause mortality varied by study country (I^2=55%); intensive treatment was associated with lower risk in the United Kingdom (HR 0.59 [95% CI, 0.35 to 0.98]), but not the Netherlands (HR 0.91 [95% CI, 0.69 to 1.21]) or Denmark (HR 1.15 [95% CI, 0.80 to 1.66]). Results for cardiovascular mortality showed a similar pattern when stratified by country, but none of the estimates were statistically significant. Both mortality and cardiovascular event rates were lower than anticipated, and there was little difference between groups in final HbA1c, blood pressure, and total cholesterol values (**Appendix B9**).[68] There was no difference in self-reported measures of general and DM-specific quality of life in ADDITION-Europe participants after 5 years followup (**Appendix B9**).[138]

Analyses of 1,161 ADDITION-Denmark participants found no difference between intensive and standard treatment in measures of neuropathy after 6 years (**Appendix B9**).[135] In the ADDITION-Netherlands trial (n=498), there was no difference between intensive and standard treatment in most measures of quality of life, based on the SF-36 and DM-specific scales. However, intensive treatment was associated with slightly worse (lower) SF-36 mental health component scores after 3 years of followup (76 vs. 80; p=0.04).[136,137]

Diabetes Not Specifically Screen-Detected

Glucose control. The prior USPSTF report found intensive glycemic control in persons with DM associated with reduced risk of various vascular events.[1] This was largely based on a meta-analysis of six trials that found reduced risk of macrovascular events (RR 0.81 [95% CI, 0.73 to 0.91]; I^2=53%), peripheral vascular events (RR 0.58 [95% CI, 0.38 to 0.89]; I^2=0%), and cerebrovascular events (RR 0.58 [95% CI, 0.46 to 0.74]; I^2=53%), but no reduction in cardiac events (RR 0.91 [95% CI, 0.80 to 1.03]; I^2=2%).[157]

We identified 11 good-quality systematic reviews on the effect of intensive glucose control on

vascular outcomes published since the prior report (**Appendix B6 and B7**).[114-124] The reviews had substantial overlap in included studies, though a few were more comprehensive (**Appendix B12**).[115,117,118] One of the largest and most recent reviews[117] analyzed evidence from 14 trials (n=28,614), including the good-quality ACCORD trial,[127] ADVANCE[80] trial, and the Veterans Affairs Diabetes Trial (VADT),[156] all published since the prior USPSTF report. Eleven of the studies included in this review were conducted in patients with established DM (duration 3 to 12 years), though three older studies in the review enrolled persons with newly or recently diagnosed DM.[158-160] Six of the included studies were judged to have low risk of bias based on assessment of allocation methods, blinding, outcome reporting, and potential for other sources of bias. The studies did not report the proportion of patients diagnosed by screening or through other methods. In four studies the glucose control target was an HbA1c was less than or equal to 6.5 percent, in four studies less than 7 percent to less than 7.5 percent, and in the remaining five studies fasting blood glucose of less than 6.6 to 6.1 mmol/L or normalization of fasting blood glucose.

The review found no difference between intensive versus standard glucose control and risk of all-cause mortality (12 studies; RR 1.02 [95% CI, 0.91 to 1.12]; I^2=30%) or cardiovascular mortality (12 studies; RR 1.11 [95% CI, 0.92 to 1.35]; I^2=46%; **Table 8)**.[117] These results are consistent with findings reported in the other systematic reviews (**Appendix B7**). Intensive glucose control was associated with lower risk of nonfatal MI versus standard control (eight studies; 4% vs. 5%; RR 0.85 [95% CI, 0.76 to 0.95]; I^2=0%). Risk of retinopathy was also reduced with intensive glucose control (seven studies; 12% vs. 14%; RR 0.80 [95% CI, 0.67 to 0.94]; I^2=59%), though heterogeneity was high and estimates were not consistently significant in the four other reviews[114,115,118,123] that assessed risk of retinopathy (**Appendix B7**). Across the 11 systematic reviews, there was no difference between intensive and standard glucose control for most other outcomes, including stroke and renal disease.

Three major trials published since the prior report each found no benefit of intensive versus standard glucose control on clinical outcomes.[126-128,156] HbA1c was less than 6.0 percent to less than or equal to 6.5 percent in the intensive glucose control groups in all three studies. In the ACCORD study (n=10,251), intensive treatment was associated with significantly increased risk of all-cause mortality (HR 1.21 [95% CI, 1.02 to 1.44]) and a nonsignificant increase in risk of cardiovascular mortality (HR 1.27 [95% CI, 0.99 to 1.63]; **Appendix B10**).[127,128] As a result, study participants receiving intensive glucose control were transitioned to standard control after about 4 years of followup. One year after the transition to standard treatment, the risk estimates were similar to earlier findings (all-cause mortality: HR 1.19 [95% CI, 1.03 to 1.38]; cardiovascular mortality: HR 1.29 [95% CI, 1.04 to 1.60]). The VADT of 1,791 primarily male United States veterans found no difference between intensive and standard glucose control and all-cause mortality (HR 1.07 [95% CI, 0.81 to 1.42]) or cardiovascular (HR 1.32 [95% CI, 0.81 to 2.14]) mortality, though estimates were in the same direction as ACCORD.[156] Participants in the VADT trial had somewhat higher baseline HbA1c levels than those in ACCORD (9.4% vs. 8.3%), longer duration of DM (12 years vs. 10 years), and similar rates of previous cardiovascular events (40% vs. 35%). The ADVANCE trial, which enrolled 11,140 participants with less severe DM (mean HbA1c 7.5%) and of shorter duration (mean 8 years), also found no difference between intensive and standard treatment in all-cause mortality (RR 0.93 [95% CI, 0.83 to 1.05]) or cardiovascular (RR 0.88 [95% CI, 0.74 to 1.03]) mortality (**Appendix B10**).[126]

The ACCORD-Eye study found a significant reduction in progression of retinopathy with intensive glucose control (RR 0.70 [95% CI, 0.55 to 0.89]) compared with standard control in a subgroup of ACCORD participants (n=2,856),[143] though there was no difference between groups for this outcome in the VADT study (RR 0.86 [95% CI, 0.66 to 1.13]).[156] There were no differences in either the ACCORD and VADT studies between intensive and standard glucose control in risk of other vascular outcomes such as stroke, congestive heart failure, or sudden death (**Appendix B10**).[127,128,156]

Long-term post-trial monitoring data from the good-quality U.K. Prospective Diabetes Study (UKPDS) has also been published since the prior USPSTF report.[154] Although the UKPDS concluded in 1997, continued followup of participants has been performed to determine the long-term effects of intensive glucose (target <6.0 mmol/L) and blood pressure lowering (target <150/85 mm Hg, discussed in the following section). Based on earlier UKPDS results, the 2003 USPSTF report noted a nonsignificant reduction in risk of MI with intensive glucose control (RR 0.84 [95% CI, 0.71 to 1.0]), with no difference between intensive and standard groups for other cardiovascular outcomes.[77] With additional followup (mean 10 years) intensive treatment was associated with reduced risk of all-cause and DM-related mortality (RR 0.88 [95% CI, 0.82 to 0.94] and RR 0.85 [95% CI, 0.76 to 0.94]), and risk of MI remained reduced (RR 0.86 [95% CI, 0.78 to 0.95]; **Appendix B10**).[154]

A separate analysis of data from the ADVANCE trial found no difference between intensive and standard glucose control and risk of various cancers or cancer mortality (**Appendix B10**).[146] These results were consistent with those reported in a meta-analysis of the ACCORD, UKPDS, and VADT studies (RR 1.03 [95% CI, 0.83 to 1.29]).[161] An analysis of a random subset of ACCORD participants found no clinically meaningful difference in quality of life between intensive and standard treatment in SF-36 and DM-specific quality of life measures,[144] and the ACCORD-Bone substudy found no difference in risk of fractures or falls [139] (**Appendix B10**).

Blood pressure control. The 2008 USPSTF report found more intensive blood pressure control associated with reduced cardiovascular morbidity compared with standard treatment.[1] This conclusion was based on four studies[72-76] included in the 2003 USPSTF report,[77] as well as a subsequent meta-analysis of comparative effects of antihypertensive treatments on mortality and cardiovascular events in persons with and without DM (described in Contextual Question 4).[71] We identified two additional good-quality systematic reviews published since the 2008 report (**Appendix B6 and B7**).[125,134] These two reviews included five trials (n=8,332) and 13 (n=37,736) trials of more versus less intensive blood pressure lowering, respectively, both of which included data from the blood pressure lowering arms of ADVANCE and ACCORD (discussed below). The larger review excluded studies with an achieved SBP of greater than 140 mm Hg in the standard treatment group, studies that reported less than 3 mm Hg difference between intensive and standard treatment groups and studies of patients with type 1 diabetes.[125] The review also included two studies of persons with IFG, one of which was included in the previous USPSTF report[14] and the other,[104] published since the prior report, is included in Key Question 6. Ten of the studies were assessed as having a low risk of bias, using quality assessment based on method of treatment allocation and blinding. Baseline HbA1c in participants in the included studies ranged from 6 percent to 11.5 percent in 10 studies reporting

HbA1c levels and duration of followup ranged from 2 to 7 years.

Results of the two meta-analyses are summarized in **Table 9**. The number of studies pooled for specific outcomes varied slightly between the reviews, but risk estimates were generally consistent. Intensive blood pressure control (achieved SBP ≤135 mm Hg) was associated with reduced risk of all-cause mortality (RR 0.90 [95% CI, 0.82 to 0.98]; I^2=0%) compared with standard control (achieved BP ≤140 mm Hg).[125] Intensive blood pressure treatment was also associated with reduced risk of stroke (RR 0.83 [95% CI, 0.73 to 0.95]; I^2=27%[125] and RR 0.61 [95% CI, 0.48 to 0.79]; I^2=0%[134]), though the effect was most pronounced when lower blood pressure targets were achieved (SBP ≤130 mm Hg; RR 0.53 [95% CI, 0.38 to 0.75]; I^2=0%).[125] There was no difference between intensive and standard blood pressure control in risk of cardiovascular mortality, MI, or heart failure.[125,134]

The two major new trials on effects of more versus less intense blood pressure control on clinical outcomes in persons with DM are the good-quality ACCORD-BP[79] and ADVANCE[80] trials (**Appendix B10)**. Long-term, post-treatment followup of the U.K. Prospective Diabetes Study (UKPDS) has also become available.[155] The studies had important differences in design and patient demographics. The ACCORD-BP trial included 4,733 participants randomized to intensive (target SBP <120 mm Hg) or standard (target SBP <140 mm Hg) blood pressure control. Mean blood pressure at baseline was 139/76 mm Hg. After 1 year of treatment, participants in the intensive arm were taking an average of three blood pressure medications compared with two blood pressure medications in the standard group; the proportion of patients taking an ACE inhibitor (60% vs. 52%), angiotensin II receptor blockers (ARBs; 41% vs. 30%), or either (90% vs. 80%) was slightly higher in the intensive therapy group compared with the standard therapy group. Mean blood pressures were 119/64 mm Hg versus 134/71 mm Hg, respectively at 1 year and blood pressure control remained stable through 5 years of followup.[79] The ADVANCE trial (n=11,140) did not utilize a specific blood pressure target. Rather, participants were randomized to a fixed-dose ACE inhibitor-diuretic combination (perindopril plus indapamide) or placebo added onto their existing therapy. Mean baseline blood pressures were 145/81 mm Hg in both groups. At 5 years followup, mean blood pressure was 136/73 mm Hg in the perindopril/indapamide group and 140/73 mm Hg in the placebo group. Thus, the "intensive" group in ADVANCE achieved marginally higher SBP and DBP readings than the "standard" ACCORD group. In the UKPDS cohort, differences in blood pressures between the intensive and standard blood pressure control groups at the beginning of the posttrial monitoring period (143/79 mm Hg vs. 152/82 mm Hg; p<0.001) did not persist with longer followup, and no attempt was made to maintain treatments.[155] All three studies used different composite outcomes as the primary outcome, but also reported results for individual outcomes (**Appendix B10**).

Results from the four studies included in the prior reports and the ACCORD and ADVANCE trials are summarized in **Table 10**. There are some inconsistencies between the ACCORD and ADVANCE trials. The ADVANCE trial found intensive blood pressure control associated with decreased risk of all-cause (RR 0.87 [95% CI, 0.76 to 0.98]) and cardiovascular (RR 0.82 [95% CI, 0.69 to 0.98]) mortality.[80] The ACCORD trial found no differences between intensive versus standard treatment in risk of all-cause mortality (RR 1.11 [95% CI, 0.89 to 1.38]) or cardiovascular mortality (RR 1.04 [95% CI, 0.73 to 1.48]), but decreased risk of fatal and nonfatal stroke (RR 0.58 [95% CI, 0.39 to 0.88]).[79] Long-term, post-trial followup of UKPDS

participants found no difference between intensive versus standard therapy in risk of all-cause mortality (RR 0.89 [95% CI, 0.75 to 1.06]) or stroke (RR 0.77 [95% CI, 0.55 to 1.07]).[155] None of the studies reported differences between intensive and standard blood pressure control in other outcomes, including MI, heart failure, renal failure, retinopathy, neuropathy, and quality of life (**Table 10** and **Appendix B10**).

Some potential reasons for the differences between the results of the ACCORD and ADVANCE trials include the use of different types of interventions (blood pressure treated to target versus the addition of a specific medication combination), differences in the blood pressures achieved with the intervention, and others (e.g., differences in populations).[162,163] In addition, the annual rate for the primary outcome (cardiovascular mortality, nonfatal MI, and nonfatal stroke) in the standard treatment group of the ACCORD study was only about half the anticipated rate (actual rate 2%/year vs. anticipated rate 4%/year), potentially reducing statistical power.[79]

Lipid control. The previous USPSTF report[1] did not include any studies of intensive versus standard lipid control in persons with DM, though it did include studies comparing the differential effects of lipid-lowering therapy in persons with and without DM (see Contextual Question 4). We identified two trials published since the prior USPSTF report on effects of additional lipid-lowering therapies in persons with DM (**Appendix B10**). The ACCORD Lipid substudy analyzed 5,518 participants randomized to simvastatin plus fenofibrate versus simvastatin plus placebo; it did not utilize specific lipid targets.[129] HbA1c was 8.3 percent in both groups at baseline and lipid levels were similar (total cholesterol approximately 175 mg/dl and LDL approximately 100 mg/dl). There was no significant difference in all-cause (RR 0.91, [95% CI, 0.76 to 1.10]) or cardiovascular (RR 0.86 [95% CI, 0.66 to 1.13]) mortality, or most individual (e.g., stroke, MI, heart failure) or composite outcomes. However, lipid lowering was associated with a reduction in progression of retinopathy in a subgroup of 2,856 ACCORD participants (RR 0.63 [95% CI, 0.45 to 0.89]; Appendix B10).[143] The second study (MEGA) enrolled persons with and without DM (see Contextual Question 4).[84] Study participants with DM (n=1,746; mean HbA1c 6.9%) were randomized to pravastatin plus diet or diet alone. There was no difference between groups in risk of all-cause or cardiovascular mortality, stroke, cerebral infarction, or composite vascular outcomes (**Appendix B10**).

Multifactorial interventions. The 2008 USPSTF evidence report did not include studies of more versus less intensive multifactorial interventions for glucose, blood pressure, or lipid lowering in persons with DM.[1] We identified three good-quality studies[130,131,152,153] and one fair-quality study[148] (reported in five publications) on the effects of combined glucose, blood pressure, and lipid lowering on health outcomes (**Table 11** and **Appendix B10**). Duration of followup ranged from 3 to 15 years (median 6 years). The multifactorial interventions varied in studies and were based on treatment algorithms[148,152,153] or recommended protocols.[130] For example, the ADVANCE trial added perindopril plus indapamide combination for blood pressure lowering and gliclazide modified release (MR) for glucose control in the intensive group, compared with placebo and physician-determined glucose-lowering regimens in the standard group.[130] In the Steno-2 trial, participants in the intensive control group received an ACE inhibitor (or an ARB, if an ACE inhibitor was contraindicated), aspirin, multivitamin supplement, diet and exercise recommendations and, if HbA1c levels were not adequately controlled with diet and exercise alone, an oral hypoglycemic. In the trials, adjustments to blood pressure and glucose lowering

agents could be made based on the treatment algorithms. The trials also varied in their use of targets. For example, the ADVANCE trial evaluated the addition of an ACE inhibitor-diuretic drug combination without a blood pressure target.[130] In the three studies that utilized blood pressure targets, the Stop Atherosclerosis in Native Diabetics Study (SANDS) Trial used a lower SBP target (<115 mm Hg) than the other two studies (<130 mm Hg).[131,148,152,153] Although glucose, blood pressure, and lipid levels were reduced with intensive treatment in all of the studies, targets were generally not met in any study (**Table 11**).

The intensive multifactorial intervention was associated with reduced risk of all-cause mortality in the ADVANCE trial (RR 0.83 [95% CI, 0.70 to 0.99])[130] and the Steno-2 trials (RR 0.60 [95% CI, 0.40 to 0.90]).[131] The multifactorial intervention was also associated with lower risk of cardiovascular mortality in these trials (RR 0.76 [95% CI, 0.60 to 0.98] and RR 0.47 [95% CI, 0.23 to 0.98], respectively). However, results from the fair-quality Japanese Elderly Diabetes Intervention Trial (JEDIT) trial (n=1,173), which enrolled an older population than the other studies (mean age 72 years vs. 55 years to 66 years) with a longer duration of DM at baseline (approximately 17 years vs. 8 years in the ADVANCE trial), found no difference between intensive and standard groups for any outcome after 6 years.[148] Absolute event rates were lower in this study than in the ADVANCE and Steno-2 trials. There was an 8 percent incidence of all-cause mortality in the JEDIT trial, compared with 15 percent and 40 percent in the ADVANCE and Steno-2 trials after 5 years and 13 years, respectively. Risk estimates could not be calculated for this study, making comparisons with the other trials difficult. Both the ADVANCE and Steno-2 trials found the multifactorial intervention associated with reduced risk of nephropathy (RR 0.68 [95% CI, 0.51 to 0.89] and RR 0.44 [95% CI, 0.24 to 0.77]).[130,131] The good-quality SANDS trial found no difference between intensive and standard groups in incidence of cardiovascular events, a composite outcome that included fatal coronary heart disease, fatal and nonfatal MI and stroke, and need for revascularization procedures (RR 1.35 [95% CI, 0.55 to 3.29]).[152] Results for other outcomes were inconsistent between trials and are reported in **Appendix B10**.

Aspirin. The previous USPSTF report found aspirin use in persons with DM associated with relatively small benefit in reducing the risk of cardiovascular events.[1] This conclusion was based on data from DM subgroups in a meta-analysis of nine studies (n=5,000 patients approximately) that found aspirin use associated with a slightly reduced risk of vascular events (including cardiovascular events and stroke).[85] Based on the data provided in the meta-analysis, we calculated a pooled RR of 0.93 (95% CI, 0.83 to 1.07). The prior report also included two studies published subsequent to the meta-analysis that reported DM subgroup data. These studies found no effect of aspirin use versus nonuse on risk of cardiovascular events,[86,87] though there was a significant reduction in risk of stroke in women taking aspirin in one study (RR 0.83 [95% CI, 0.69 to 0.99]).[87]

We identified one fair-quality trial (in two publications[149,150]) and two good-quality systematic reviews[132,133] published since the previous USPSTF report on the association between aspirin use and health outcomes in persons with DM. One other study of aspirin use versus nonuse was excluded because it included persons with type 1 diabetes and did not stratify results according to population.[164]

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial randomized 2,539 persons with diabetes to daily aspirin use or nonuse (**Appendix B10**).[149,150] After 4 years, there was no difference in risk of atherosclerotic events, a composite outcome that included coronary heart disease, MI, and stroke, in others (68/1262 [5%] vs. 86/1277 [7%]; HR 0.80 [95% CI, 0.58 to 1.10]). There was also no significant difference in risk of individual outcomes between groups, with the exception of coronary and cerebrovascular mortality (1/1262 [0.08%] vs. 10/1277 [0.8%]; HR 0.10 [95% CI, 0.01 to 0.79]), though the absolute incidence for all outcomes was low.

Consistent with the meta-analysis included in the prior USPSTF report, a more recent good-quality systematic review[132] of six studies (n >10,000 persons with DM), including the JPAD trial, found no difference between aspirin use and nonuse and risk of all-cause mortality (four studies; RR 0.93 [95% CI, 0.82 to 1.05]; I^2=0%), cardiovascular mortality (four studies; RR 0.94 [95% CI, 0.72 to 1.23]; I^2=57%), major cardiovascular events (five studies; RR 0.90 [95% CI, 0.81 to 1.0]; I^2=0%), MI (six studies; RR 0.86 [95% CI, 0.61 to 1.21]; I^2=62%) and stroke (five studies; RR 0.83 [95% CI, 0.60 to 1.14]; I^2=53%) though some heterogeneity was present in most analyses (**Appendix B7**). Sensitivity analyses found no effect based on aspirin dose or treatment duration for most outcomes. However, risk of stroke was significantly reduced when analyses were restricted to aspirin dose <100 mg/day (p=0.02), to studies greater than 5 years duration (p=0.01), and in patients who adhered to aspirin therapy (p=0.02). A second good-quality systematic review that included most of the same trials reported very similar risk estimates and found no significant difference between aspirin use and nonuse for any outcome (**Appendix B7**).[133]

Persons with IFG or IGT. We identified one study of intensive versus standard lipid therapy in persons with IFG.[84] It was a subgroup analysis from the large Japanese MEGA trial[151] of persons with hypercholesterolemia (mean total cholesterol 243 mg/L and LDL cholesterol 156 mg/L). It found no differences between diet plus pravastatin versus diet alone on risk of health outcomes, including all-cause mortality, stroke and coronary heart disease after 5 years followup (**Appendix B10**). We identified no study on effects of intensive glucose or blood pressure control versus standard control in persons with IFG or IGT.

Key Question 6. What Are the Harms of More Intensive Interventions Compared With Traditional Control in Adults With Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance?

Summary

The prior USPSTF report did not include evidence on harms associated with more versus less intensive glucose, blood pressure, or lipid control or with aspirin use versus nonuse.[1] Four good-quality systematic reviews found intensive glucose control associated with increased risk of severe hypoglycemia.[115,117,121,123] More intensive blood pressure lowering therapy was associated with increased risk of serious adverse events in the ACCORD study (RR 2.58 [95% CI, 1.70 to

3.91])[79] but not the ADVANCE study (RR 1.02 [95% CI, 0.72 to 1.42]).[80] Results for other outcomes were inconsistent between trials and are reported in **Appendix B10**. Aspirin was associated with an increased risk of major and gastrointestinal bleeding in a good-quality systematic review, though heterogeneity was high (I^2=66% and 72%) for both estimates (RR 3.02 [95% CI, 0.48 to 19] and RR 2.12 [95% CI, 0.63 to 7.08]), respectively.[133]

Evidence

The previous USPSTF report did not include evidence on harms associated with more versus less intensive glucose, blood pressure, or lipid control or with aspirin use versus nonuse,[1] and harms were not reported in most trials published since the prior report (**Appendix B10**).

Glucose lowering therapy was associated with increased risk of severe hypoglycemia (four systematic reviews; pooled RR range 1.76 to 2.39; **Appendix B7**).[115,117,121,123] Definitions for severe hypoglycemia varied across studies, and included documentation of glucose <50 mg/dL and events requiring medical assistance (ranging in severity from cognitive impairment to coma or seizure). The ACCORD and VADT studies both also found intensive therapy associated with increased risk of serious nonhypoglycemia adverse events requiring medical intervention (2.4% vs. 1.6%, RR 1.44 [95% CI, 1.09 to 1.90] and 24% vs. 18%, RR 1.37 [95% CI, 1.14 to 1.65]).[128,156] Serious adverse events were also more likely in the intensive blood pressure lowering group of the ACCORD-BP trial (3% vs. 1%, RR 2.58 [95% CI, 1.70 to 3.91])[128] but not in the ADVANCE blood pressure lowering trial (RR 1.02 [95% CI, 0.72 to 1.42]).[80] The ACCORD Lipid trial found no significant difference between intensive lipid-lowering and standard treatment in rates of serious adverse events (RR 1.29 [95% CI, 0.96 to 1.74]).[129] The use of an intensive multifactorial intervention resulted in higher rates of serious adverse events in the SANDS trial (27% vs. 15%, RR 1.72 [95% CI, 1.21 to 2.47])[152] but not in incidence of severe hypoglycemia in the Steno-2 trial (RR 0.71 [95% CI, 0.34 to 1.51]).[131]

In the JPAD trial of aspirin use versus nonuse, serious adverse events were rare, with no difference in incidence between aspirin use and nonuse groups.[149,150] A good-quality systematic review of six studies of aspirin use versus nonuse found aspirin increased risk of major bleeding (two studies; RR 3.02 [95% CI, 0.48 to 19]; I^2=66%) and GI bleeding (three studies; RR 2.12 [95% CI, 0.63 to 7.08]; I^2=72%) events in persons with DM, though risk estimates were not statistically significant and heterogeneity was high.[133]

Key Question 7. Do Interventions for Impaired Fasting Glucose or Impaired Glucose Tolerance Delay Prevent the Progression to Type 2 Diabetes?

Summary

The previous USPSTF report[1] found lifestyle and pharmacological interventions associated with decreased risk of progression to DM in patients with IFG or IGT.[1] Sixteen studies (in 18 publications) published since the prior report evaluated the effects of multifactorial, lifestyle, and

pharmacologic interventions on risk of subsequent DM in patients with IFG or IGT at baseline.[98, 101-104,110,165] Two studies of multifactorial interventions found no effect on risk of progression to DM, though the estimate was imprecise in one study (RR 0.89 [95% CI, 0.78 to 1.02] and RR 0.08 [95% CI, 0.00 to 1.42]).[166,167] Six studies assessed lifestyle interventions, with three of the studies reporting reduced risk of progression to DM (RRs ranged from 0.26 to 0.55) and the other three studies reporting a nonstatistically significant effect (RR 0.45 [95% CI, 0.17 to 1.21]; RR 0.51 [95% CI, 0.24 to 1.11]; and RR 0.36 [95% CI, 0.12 to 1.11]).[102,110] The pooled risk estimate for progression to DM with lifestyle interventions, including four studies from the prior USPSTF report, was 0.53 (95% CI, 0.39 to 0.72; I^2=88%).

Eight studies published since the prior USPSTF report evaluated effects of various pharmacologic interventions on progression to DM in patients with IFG or IGT.[98,101,103,105,106,109, 165,168] TZDs (three trials; RR 0.50 [95% CI, 0.27 to 0.92]; I^2=92%) and alpha-glucosidase inhibitors (four trials; 0.64 [95% CI, 0.45 to 0.90]; I^2=66%) were more effective than placebo at reducing risk of progression to DM. One trial found valsartan (RR 0.90 [95% CI, 0.85 to 0.95]) but not nateglinide (RR 1.05 [95% CI, 0.99 to 1.11]) associated with decreased risk of progression to DM.[103,104] Finally, one study reported that low-dose sulphonylurea added to lifestyle counseling was not effective in delaying progression to diabetes.[168]

Evidence

The previous USPSTF report[1] included a meta-analysis that found lifestyle interventions (five studies, n=3,490; duration of followup 3 to 6 years) or pharmacological interventions (seven studies, n=12,519, duration of followup 2 to 4 years) associated with decreased risk of progression to DM in patients with IFG or IGT (pooled RRs 0.48 [95% CI, 0.40 to 0.58]; I^2=34% and 0.65 [95% CI, 0.51 to 0.83]; I^2=74%).

We identified 16 studies (in 18 publications) published since the prior report on the effect of interventions on progression to DM in patients with IFG or IGT (**Table 12**, **Appendix B13, B14 and B15**).[98,101-107,109,110,165-172] In these studies, progression to diabetes was generally assessed by means of fasting plasma glucose, 2-hour plasma glucose, or oral glucose tolerance tests using WHO criteria (FPG >7.0 mmol/L [126 mg/dL] or 2-hour plasma glucose or OGTT >11.0 mmol/L [200 mg/dL]). Interventions included intensive multifactorial interventions (two studies),[166,167] lifestyle interventions (six studies),[102,110] and pharmacologic interventions (eight studies).[98,101,103-106,109,165,168] Studies were conducted in the United States,[98,165,172] Canada,[109] Europe,[105,167-169,171] and Asia[101,102,107,110,170]; one multicenter study was conducted in 40 counties.[103,104] Treatment duration ranged from 6 months to 6 years, with followup extending up to 23 years (median or mean followup ranged from 6 months to 9 years). All studies enrolled patients with IFG or IGT at baseline, with several studies also requiring the presence of one or more other risk factors for DM,[98,103,104,109,167,172] for example, baseline BMI above a specific threshold.[98,107,166,169,171,172] Mean ages of participants ranged from 45 to 65 years, and mean BMI ranged from 25.7 kg/m^2 to 34.5 kg/m^2. In studies reporting race and ethnicity, enrollees were primarily white,[103,104,109,165,172] though one study[98] enrolled 49 percent non-white participants. Three trials were rated good-quality[101,103,104,109]; the other 13 trials and the cohort study were rated as fair-quality. Methodological shortcomings of the fair trials included unclear methods of randomization and allocation concealment,[98,102,110] baseline differences between groups,[105]

unclear blinding or failure to blind,[98,102,110] and lack of intention-to-treat analysis.[106,166, 167,170,171]

Lifestyle Interventions

The previous USPSTF report included four studies of lifestyle interventions providing new evidence, all of which found lifestyle interventions associated with decreased risk of progression to DM versus usual care over followup periods ranging from 3 to 6 years.[2] Relative risks ranged from 0.32 (95% CI, 0.11 to 0.96) to 0.62 (95% CI, 0.42 to 0.92), with a pooled risk estimate of 0.48 (95% CI, 0.40 to 0.58).

Six fair-quality studies (in seven publications) published since the previous USPSTF report assessed the effect of lifestyle interventions on risk of progression to DM (**Table 12, Appendix B13**).[102,110] Studies were conducted in patients with IGT in Japan, China, and Europe. Interventions varied across studies and involved combinations of individual and group diet and exercise counseling sessions. The duration of interventions also varied substantially, from a 1-month intervention based in a wellness center with a 4-day followup intervention one year later to a 6-year intervention. Duration of followup ranged from 3 to 23 years. The Da Qing trial, conducted in China, reported the highest rate of progression to DM (73% in the intervention group and 90% in the comparison group) than the other studies (6% to 11% in the intervention groups and 12% to 24% in the comparison groups), consistent with its longer duration of followup and selection of patients with mean BMI greater than 25 kg/m^2.[102,110]

Three of the studies, including the Da Qing trial, found the lifestyle intervention associated with decreased risk of progression to DM (RR 0.65 [95% CI, 0.43 to 0.97][107 102]; RR 0.86 [95% CI, 0.80 to 0.92] at 20 years[102] and HR 0.55 [95% CI, 0.40 to 0.76] at 23 years[107,110]; and RR 0.26 [95% CI, 0.10 to 0.65][171]), while the other three studies favored the lifestyle intervention but failed to reach statistical significance (RR 0.45 [95% CI, 0.17 to 1.21][169]; RR 0.51 [95% CI, 0.24 to 1.11][170]; and RR 0.36 [95% CI, 0.12 to 1.11][172]). The pooled RR, including six new studies and four studies included in the prior report, was 0.53 (95% CI, 0.39 to 0.72; I^2=88%; **Figure 4**).[102,110,169] Sensitivity analysis excluding the study with the longest followup (23 years; the Da Qing trial) showed similar results (pooled RR 0.53 [95% CI, 0.44 to 0.63]; I^2 =25%), as did analysis using the profile likelihood estimate (0.57 [95% CI, 0.43 to 0.70], I^2=67%).[4-7,107,169-172]

Pharmacologic Interventions

Eight studies (three of good quality and five of fair quality) published since the previous USPSTF report assessed the effect of pharmacologic intervention on risk of progression to DM in patients with IFG or IGT. (**Table 12, Appendix B13**).[98,101,103,105,106,109,165,168] Interventions included several classes of medications for glycemic control (8 trials), as well as the anti-hypertensive medication valsartan (1 trial), an angiotensin receptor blocker. Diabetic medication classes included biguanides, TZDs (three trials), alpha-glucosidase inhibitors (three trials), meglitinides, sulphonylureas, and glucagon-like peptide -1 (GLP-1) agonists, or combinations of these medications. One study used a prospective cohort design[165] and the rest were RCTs. Followup ranged from 6 months to 5 years.

Metformin. The previous USPSTF report[1] included the good-quality Diabetes Prevention

Program (DPP) study and fair-quality Indian Diabetes Prevention Program (IDPP) study; both reported the effect of metformin on progression to DM.[4,7] The DPP study (n=3,234; 49% were ages 45 to 59 years; 32% male) randomized patients to lifestyle modification, metformin, or placebo and followed patients for 3 years. The IDPP study (n=531; mean age 46 years; 79% male) also randomized patients to lifestyle modification, metformin, or no intervention.[7] The overall incidence of progression to DM was 8/100 person-years in the metformin group and 11/100 person-years in the placebo group (risk reduction 31% [95% CI, 24% to 51%]) in the DPP study.[4] In the IDPP, incidence of DM was 41 percent in the metformin group and 55 percent in the no intervention group after 3 years of followup (relative risk reduction 26% [95% CI, 19.1% to 35.1%]). Lifestyle modification resulted in greater effects than metformin relative to placebo or no intervention in both studies (risk reduction 58% [95% CI, 48% to 66%][4] and 29% [95% CI, 21% to 37%][7]).

We identified one new study of metformin reporting progression to DM.[166] A small (n=181) Chinese study employed a staged intensive intervention in which participants with isolated IFG or combined IFG and IGT received metformin 250 mg/three times per day and participants with isolated IGT received acarbose 50 mg/three times per day, with all participants also receiving aspirin and pharmacologic treatment for hypertension and dyslipidemia. In the group receiving metformin, no intervention participant progressed to DM versus five control participants (0% vs. 12.2%; RR 0.08 [95% CI, 0.00 to 1.42]).

TZDs. The previous USPSFT report included one study on the effect of TZDs on progression to DM. The large (n=5,269) good-quality DREAM trial used a 2x2 factorial design to randomize patients to rosiglitazone (a TZD) or placebo and ramipril (an ACE inhibitor) or placebo, with followup for 3 years. It found no effect of ramipril on risk of progression to DM (17% vs. 19%; RR 0.91 [95% CI, 0.77 to 1.08]); rosiglitazone was associated with decreased risk (11% vs. 25%; RR 0.38 [95% CI, 0.31 to 0.47]).

Two fair-quality studies (n=887) published since the previous USPSTF report, assessed the effect of TZDs on risk of progression to DM in patients with IGT (**Table 12, Appendix B13**).[98, 106] One study required patients to have at least one other risk factor (e.g., BMI >25 kg/m^2, family history, gestational diabetes, polycystic ovarian syndrome, or African American ethnicity) for DM.[98] The studies were conducted in India[106] and the United States.[98] The Indian Diabetes Prevention Program-2[106] (n=367) and a study by Defronzo et al.[98] (n=602) compared pioglitazone versus placebo for a median of 3 years and 2 years, respectively. The dosing of medications ranged from 15 mg to 45 mg for pioglitazone. One trial found TZDs associated with decreased risk of progression to DM versus placebo (5.0% vs. 16.7%, RR 0.30 [95% CI, 0.17 to 0.52])[98], while the other trial found no effect (29.8% vs. 31.6%, RR 0.94 [95% CI, 0.69 to 1.28]).[106] The NNT to prevent one patient from developing DM was 8 over 2 years in the study by Defronzo et al[98] and 52 over 3 years in the IDPP-2 trial.[106] The pooled estimate for the effect of TZDs on progression to DM, including the two new trials and the earlier DREAM trial,[15] was 0.50 (95% CI, 0.27 to 0.92), but statistical heterogeneity was substantial (I^2 = 92%; **Figure 5**).[15, 98,106,107] Analysis using the profile likelihood method slightly reduced heterogeneity (RR 0.51 [95% CI, 0.23 to 1.06]; I^2=89%), though this result was no longer statistically significant. Removing results of the IDPP-2 trial,[106] which was conducted in India in mostly male participants, eliminated much of the heterogeneity (I^2=36%) with RR 0.42 (95% CI, 0.37 to

0.47).[15,98] Stratified analyses showed that rosiglitazone and pioglitazone were similar in their effects.

Alpha-glucosidase inhibitors. The previous USPSTF report included two studies on the effects of alpha-glucosidase inhibitors on risk of progression to DM in patients with IFG or IGT.[111,173] Both studies assessed acarbose versus placebo, with followup durations of 16 weeks[173] and 3.3 years.[111] The longer study by Chiasson et al. found acarbose associated with reduced risk of progression to DM (32% vs. 42%; RR 0.78 [95% CI, 0.68 to 0.90]), while the shorter duration trial reported a point estimate in favor of acarbose that failed to reach statistical significance (5.6% vs. 9.5%; RR 0.59 [95% CI, 0.24 to 1.46]).

Two new studies (1 good- and 1 fair-quality) assessed the effect of alpha-glucosidase inhibitors on incidence of DM in persons with IFG/IGT (**Table 12, Appendix B13**).[101,105] The good-quality trial (n=1,778) found voglibose 0.2 mg/day associated with decreased risk of progression to DM versus placebo after a mean of 3 years (5.5% vs. 12%, RR 0.46 [95% CI, 0.34 to 0.64]).[101] The fair-quality study (n=118) found no statistically significant difference between acarbose 150 mg/day versus placebo in risk of progression to DM after 3 years (18% vs. 24%, RR 0.76 [95% CI, 0.38 to 1.53]),[105] but was underpowered due to difficulties in recruitment and had high rates of dropout due to medication side effects. The pooled estimate for the effect of alpha-glucosidases, including these two trials as well as two studies from the prior report, was 0.64 (95% CI, 0.45 to 0.90).[101,105,111,173] Although statistical heterogeneity was present (I^2=66%; **Figure 6**), estimates favored the alpha-glucosidase in each trial. Pooling the three trials of acarbose[105,111,173] eliminated the heterogeneity (pooled RR 0.77 [95% CI, 0.68 to 0.89]; I^2=0%).

Nateglinide and valsartan. The large (n=9,306), good-quality NAVIGATOR trial was a multicenter study in 40 countries with median followup of 5 years that used a 2x2 factorial design to randomize patients with IGT and at least one other risk factor for cardiovascular disease to nateglinide (a newer insulin secretagogue) versus placebo and valsartan versus placebo.[103,104] Nateglinide was not associated with decreased risk of DM over 5 years (RR 1.05 [95% CI, 0.99 to 1.11]), but valsartan was associated with decreased risk (33% vs. 37%, RR 0.90 [95% CI, 0.85 to 0.95]; **Table 12, Appendix B13**).

Sulphonylureas. One fair-quality multicenter trial conducted in Sweden assessed the effect of 1 mg/day glimepiride on progression to diabetes compared with placebo.[168] The Nepi Antidiabetes Study (n=274) enrolled patients ages 40 to 70 years with IFG and reported incidences of progression to diabetes of 30.1 percent in the intervention group and 39.9 percent in the placebo group over a mean followup of 3.7 years (RR 0.76 [95% CI, 0.55 to 1.05]).

Combination pharmacologic therapies. One good-quality RCT and one fair-quality cohort study assessed the effect of combination pharmacologic therapy on prevention of DM in patients with IFG or IGT.[109,165] The CANOE trial[109] (n=207) compared low-dose metformin plus rosiglitazone versus placebo and followed patients for a median of 4 years. The incidence of DM in the combination drug therapy group was 14 percent compared with 39 percent in the placebo group (RR 0.34 [95% CI, 0.20 to 0.59]). The cohort study (n=105)[165] compared pioglitazone plus metformin (with and without exenatide) with a lifestyle intervention, and reported no cases of progression to DM in patients who used TZDs versus 6 percent in the lifestyle group after 6 to 9

months.[165] Estimates were imprecise for pioglitazone plus metformin with (RR 0.13 [95% CI, 0.01 to 3.10]) and without exenatide (RR 0.15 [95% CI, 0.01 to 3.62]) versus the lifestyle intervention.[165]

Multifactorial Interventions

No trial included in the previous USPSTF report evaluated effects of multifactorial interventions versus placebo or usual care on risk of progression to DM. Two fair-quality trials published since the previous report examined the effect of multifactorial interventions consisting of intensive glucose, blood pressure, and lipid control, in addition to lifestyle counseling and aspirin (**Table 12, Appendix B13**).[166,167] The large (n=1,510) ADDITION-Denmark trial reported a not statistically significant difference in risk of progression to DM (14.1 cases/100 person-years in the intervention group versus 15.8 cases/100 person-years in the usual care group; RR 0.89 [95% CI, 0.78 to 1.02]).[167] A subgroup analysis found a stronger effect in a subgroup of patients randomized to the multifactorial intervention that also received motivational interviewing (RR 0.83 [95% CI, 0.68 to 1.00]) than in the subgroup that did not receive motivational interviewing (RR 0.95 [95% CI, 0.80 to 1.14]). A smaller (n=181) Chinese study reported a lower incidence of progression to DM in the intervention compared with the control group, though the difference was not statistically significant and the estimate imprecise due to the small number of events (0% vs. 5.8%; RR 0.08 [95% CI, 0.00 to 1.42]).[166]

Key Question 8. Do the Effects of Screening or Interventions for Screen-Detected or Early Type 2 Diabetes, Impaired Fasting Glucose, or Impaired Glucose Tolerance Vary by Subgroups, Such as Age, Sex, or Race/Ethnicity?

Summary

The prior report did not include evidence on the effect of screening or interventions in screen-detected or early DM, IFG, or IGT in subgroups.[1] No study directly evaluated whether benefits or harms of screening for DM, IFG, or IGT or subsequent interventions vary according to subgroups defined by age, sex, or race and ethnicity. Men, but not women, who underwent screening and died during followup had significantly longer life compared with those who were not screened.[49] One study comparing lifestyle modification with usual care in people with IGT found a reduction in all-cause and cardiovascular mortality in women, but not men, after 23 years followup.[110] A subgroup analysis from one study of more versus less intensive treatment in persons with DM not specifically screen-detected found no overall effect of age or race, though the highest mortality risk was in persons younger than age 65 years and in blacks.[174] Intensive lipid lowering reduced risk of a composite outcome that included cardiovascular mortality, nonfatal MI, and nonfatal stroke in men (RR 0.84 [95% CI, 0.71 to 0.997]), but not in women (RR 1.36 [95% CI, 0.98 to 1.9]) compared with standard lipid control in one study.[129] Aspirin use versus nonuse was associated with a significant reduction in risk of MI in men (RR 0.57 [95% CI, 0.34 to 0.94]), but not in women (RR 1.08 [95% CI, 0.71 to 1.65]) with no difference between the two for other cardiovascular outcomes in a good-quality systematic review.[132] We

found no evidence that effectiveness of interventions to prevent progression to DM in persons with IFG and IGT varies in subgroups.

Evidence

Screening

We did not identify any evidence from the ADDITION trial on the differential effect of screening in subgroups defined by age, sex, or race and ethnicity. The ADDITION trial focused on screening persons at higher risk for DM. The Ely study reported that in study participants who died, men who were invited to screening were significantly older than men not invited to screening at time of death (64 years vs. 61 years; p=0.01). There was no significant age difference between screened and not-screened women in age at time of death (64 years vs. 62 years; p=0.17).[49]

Treatment

Persons with screen-detected DM. We identified no subgroup analyses from the ADDITION Study on the effect of intensive versus standard multifactorial interventions in subgroups of persons with DM. Over 95 percent of persons enrolled in the ADDITION study were white Europeans and about 40% were women; mean age was 60 years.[68,69]

Persons with IFG or IGT. The long-term Da Qing study, which randomized people with IFG to lifestyle modification or usual care, found incidence of all-cause and cardiovascular mortality significantly reduced in the lifestyle group after 23 years of treatment (see Key Question 3.)[110] When these results were stratified according to sex, women had a significantly lower risk of all-cause (HR 0.46 [95% CI, 0.24 to 0.87]) or cardiovascular (HR 0.28 [95% CI, 0.11 to 0.71]) mortality. The effect in men was not significant for either outcome (HR 0.97 [95% CI, 0.65 to 1.46] and HR 0.91 [95% CI, 0.50 to 1.65]; **Appendix B3**.). Despite adjusting for baseline differences such as smoking status (a higher proportion of men were smokers, relative to women), study authors were unable to explain the disparity, though they hypothesized that poor compliance to lifestyle modification by men may have contributed to the long-term lack of effect.

Persons with DM not specifically screen-detected. The ACCORD study of more versus less intensive glucose lowering found intensive glucose lowering associated with increased risk of all-cause mortality versus standard glucose lowering (HR 1.22 [95% CI, 1.02 to 1.44). In analyses stratified by age, intensive glucose lowering therapy was associated with significantly increased risk of all-cause mortality in persons younger than age 65 years (HR 1.39 [95% CI, 1.05 to 1.82]) but not in persons ages 65 to 69 years (HR 1.23 [95% CI, 0.84 to 1.82]), 70 to 74 years (HR 1.01 [95% CI, 0.65 to 1.59]), or older than age 75 years (HR 0.90 [95% CI, 0.55 to 1.47]; **Appendix B10**).[174] Risk of all-cause mortality was similar in men (HR 1.21 [95% CI, 0.98 to 1.52]) and women (HR 1.23 [95% CI, 0.87 to 1.74]). Compared with standard glucose control, blacks in the intensive glucose lowering group had a higher risk of all-cause mortality (HR 1.60 [95% CI, 1.01 to 2.52]) than whites (HR 1.21 [95% CI, 0.98 to 1.52]), Hispanics (HR 0.60 [95% CI, 0.27 to 1.33]), and Asians or other races and ethnicities (HR 1.06 [95% CI, 0.54 to 2.07]).

In ACCORD-Lipid, men in the intensive lipid-lowering group had a significantly lower risk of experiencing a cardiovascular event (a composite outcome that included cardiovascular mortality, nonfatal MI, and nonfatal stroke; RR 0.84 [95% CI, 0.71 to 0.997]) than women (RR 1.36 [95% CI, 0.98 to 1.9]; p for interaction=0.01).[129] There was no difference in effects of intensive versus standard lipid lowering when results were stratified according to age or race (**Appendix B11**).[129] In the ADVANCE trial, no difference in composite vascular outcomes (cardiovascular mortality, nonfatal MI, nonfatal stroke, new or worsening nephropathy, or retinopathy) was found when analyses were restricted to persons younger than age 65 years, or when stratified by gender (**Appendix B10**).[80]

In a good-quality systematic review of aspirin use versus nonuse for primary prevention of cardiovascular events in persons with DM, subgroup analyses found a significant reduction in risk of MI in men (three studies; RR 0.57 [95% CI, 0.34 to 0.94]) but not in women (three studies; RR 1.08 [95% CI, 0.71 to 1.65]) with no difference between the two for other cardiovascular outcomes.[132] The review also found a decreased risk of stroke in women taking aspirin (three studies; RR 0.75 [95% CI,0.37 to 1.53]) and an increased risk in men (two studies; RR 1.11 [95% CI, 0.75 to 1.64]), though neither risk estimate was statistically significant. Analyses of heterogeneity were not reported for these subgroups.

Progression to DM

One study included in the prior report found progression to DM significantly reduced with acarbose use versus placebo; this result was consistent when stratified by age (≤55 years vs. >55 years) or gender.[111]

The ADDITION study reported rates of progression to DM stratified by IFG or IGT status, but the study did not report other subgroup differences. Comparing the intervention (lifestyle modification) and usual care groups, progression rates were higher in participants with IGT (16% vs. 18% per person-year) than those with IFG (11% vs. 13% per person-year); the effect of lifestyle modification was similar in both groups.[167] The Zensharen study also reported the intervention (lifestyle modification) to be effective compared with usual care in patients with combined IFG and IGT (6.8 cases/100 person-years vs. 12.6 cases/100 person-years; adjusted HR 0.41 [95% CI, 0.24 to 0.69]) but not in patients with isolated IFG (2.4 cases/100 person-years vs. 1.8 cases/100-person years; adjusted HR 1.17 [95% CI, 0.50 to 2.74]).[107]

Chapter 4. Discussion

Summary of Review Findings

Table 13 summarizes the evidence reviewed for this update. In two trials, one of which focused on persons at higher risk for DM, screening was associated with no effect on mortality versus no screening after ten years of followup.[49,67] Possible explanations for the lack of effect of screening on mortality include limited screening uptake, increased opportunities for DM screening across groups (both studies were conducted in the United Kingdom), improved management of cardiovascular disease risk factors contributing to decreased mortality, or inadequate length of followup for mortality outcomes. All of these factors could have attenuated any potential benefits of screening. In addition, the trials did not evaluate nonmortality clinical outcomes, which might require less lengthy followup to detect effects (e.g., microvascular outcomes). Although attending screening was associated with reduced mortality and failure to attend screening with increased mortality, such effects may be confounded by other factors associated with likelihood to attend recommended clinical services.

Evidence on harms associated with screening is limited. In one study, patients randomized to screening had greater short-term, self-reported anxiety versus those randomized to no screening,[91] but there were no negative effects on psychological measures in studies with longer followup.[92,93]

Lifestyle interventions and pharmacological interventions both appear to be effective at delaying or preventing progression to DM in persons with IFG or IGT.[4-7,15,98,101,102,105,107,110,111,168-170,172,173]

The long-term benefits of early intervention on clinical outcomes are less clear. The results of the Da Qing study, which included 23 years followup, found lifestyle modification in people with IGT significantly reduced risk of all-cause and cardiovascular mortality.[110] The results of this study are interesting, in that results from 20 years followup showed no significant benefit on these outcomes. Though the study had some limitations, including potentially limited applicability to a U.S.-relevant population, this suggests that the positive effects of early intervention may not be observed until more than 20 years following treatment. In other studies of lifestyle modification or pharmacologic treatment for screen-detected or early DM, IFG, or IGT, we found no beneficial effect of any treatment on all-cause mortality, cardiovascular mortality, or stroke. This lack of benefit in health outcomes may be due to inadequate length of followup in these studies or the fact that most pharmacologic studies included a concomitant lifestyle modification component across treatment arms that could have attenuated any potential effects of drug therapy. There was limited evidence for improvement in other health outcomes (such as nonfatal MI or cardiovascular events, renal disease, or quality of life) associated with use of certain glucose-lowering agents, antihypertensive medication, or lifestyle modification in studies with shorter followup (5 years or less),[112] and while rosiglitazone was associated with decreased renal disease, it was also associated with increased heart failure versus placebo.[99] Intensive lifestyle modification, but not metformin, led to improved quality of life scores versus placebo after 3 years.[100]

Based on data from RCTs, pharmacologic treatment of screen-detected or early DM, IFG, or IGT was associated with increased risk of withdrawal due to adverse events versus placebo,[105,111] with no clear increase in risk of serious adverse events. Many adverse events associated with pharmacologic therapy are bothersome but self-limited with discontinuation of therapy. In general, trials were not designed or powered to specifically assess the risk of serious but uncommon or rare adverse events, though evidence from studies not restricted to persons with screen-detected or early DM did not show a clear increase in risk of serious adverse events, such as lactic acidosis with metformin.[175] Specific pharmacotherapy may also be associated with an increase in specific adverse events, such as hypoglycemia with sulfonylureas or edema or congestive heart failure with TZDs.

Since the previous USPSTF report, there is now evidence from a large, good-quality trial that intensive multifactorial control aimed at glucose, blood pressure, and lipid lowering appears to offer no benefit in all-cause mortality or cardiovascular mortality or morbidity over standard control in persons with screen-detected DM after 5 years.[69] In persons with DM not specifically identified by screening, many good-quality systematic reviews found intensive glucose lowering consistently associated with no reduction in all-cause or cardiovascular mortality versus less-intensive glucose therapy.[114-124] Intensive glucose-lowering therapy was also associated with reduced risk of nonfatal MI but increased risk of severe hypoglycemia.

The 2008 USPSTF review found effects of intensive blood pressure control greater in persons with DM versus without DM, based on subgroup analyses from trials that were generally less successful at achieving lower blood pressures. Since the 2008 USPSTF review, there is more evidence on the effects of more effective, intensive blood pressure control versus standard therapy specifically in persons with diabetes. Although good-quality systematic reviews found intensive blood pressure control in persons with DM associated with reduced risk of all-cause mortality and stroke versus less intensive blood pressure control,[125,134] results from the large, recently published ADVANCE[80] and ACCORD[79] trials are more inconsistent. The ADVANCE trial found the addition of an ACE inhibitor plus diuretic associated with decreased risk of all-cause and cardiovascular mortality and the ACCORD study found no difference between a SBP target of 140 mm Hg versus 120 mm Hg in risk of all-cause or cardiovascular mortality. There is no clear evidence on the effect of more versus less intensive lipid lowering and incidence of all-cause or cardiovascular mortality. Use of intensive multifactorial interventions was associated with reduced risk of all-cause and cardiovascular mortality in two trials.[130,131] Aspirin use (vs. nonuse) had no effect on all-cause mortality, cardiovascular mortality, MI, and stroke in persons with DM.[132]

Limitations

We did not include non-English language articles, though a recent review found that limiting to English-language studies did not introduce bias into systematic review findings.[176] We identified few screening studies and only one treatment study that was conducted in a screen-detected population and evidence in all demographic subgroups is extremely limited.

Interventions included in the review for those with early or screen-detected DM and IFG or IGT

were limited to glycemic control, though the effect of blood pressure and lipid control in persons with DM is discussed in Contextual Question 4 and in Key Question 5. Studies in screen-detected populations on the effect of intensive glucose, blood-pressure, and lipid lowering were limited, thus evidence from studies in persons with DM was also included and discussed separately.

Emerging Issues and Next Steps

The ADDITION study is an ongoing study being conducted in the United Kingdom, Denmark, and the Netherlands of persons at high risk for DM. Mortality data from ADDITION-Cambridge on the effect of screening after 10 years was recently published and showed no benefit.[67] However, modeling studies that calculate a benefit to screening project patient followup for 30 or more years. Therefore, as time progresses, longer-term followup of the ADDITION study would be informative for understanding benefits and harms of screening.

Relevance for Priority Populations

The ADDITION trial was conducted in a population at high risk for DM, but there is little clear evidence on how screening for DM, IFG, or IGT differs according to age, sex, or race and ethnicity. The only early intervention study to find an effect on mortality was the Da Qing study conducted in people with IGT, which found in a subgroup analysis that women, but not men, in a lifestyle modification group had a significantly lower risk of all-cause or cardiovascular mortality after 23 years followup compared with usual care.[110] In a subgroup analysis from the ACCORD study of intensive glucose lowering for DM not specifically screen-detected, there was no overall effect of age or race, but all-cause mortality risk was highest in persons younger than age 65 years and in blacks,[172] while use of intensive lipid lowering significantly reduced risk of cardiovascular events in men but not women.[126] The ADVANCE trial of intensive blood pressure lowering found no differential effect on vascular outcomes when results were stratified by age or sex.[79,174,129,80] Aspirin use in persons with DM was associated with reduced risk of MI in men, and associated with a not statistically significant reduction in risk of stroke in women based on a systematic review of three studies.[132]

Future Research

We identified a number of important research gaps. Screening studies in U.S. populations in which the prevalence of undiagnosed DM (and IFG and IGT) is likely to be higher than the 3 percent identified in the ADDITION-Cambridge and Ely studies would be more applicable for informing screening decisions in the United States. There is also little evidence on the effect of screening on ethnic and racial minorities whose prevalence of DM is higher than in those of white, European ancestry. More research is also needed to identify optimal treatment strategies for screen-detected DM, given the findings of the treatment phase of the ADDITION trial.[69]

Recently published studies using data from participants in ADDITION-Denmark validate DM

susceptibility allele variants suggesting a role for the pathogenesis of pancreatic B-cell dysfunction.[177] This and other ongoing genomic research[178] related to glucose dysregulation may play a role in the future selection of DM treatments and treatment targets.

Long-term followup of studies of early lifestyle interventions in people with screen-detected DM, IFG, or IGT is needed to confirm the findings of the Da Qing study.

Conclusions

Screening for DM did not improve mortality after 10 years followup in two trials[49,67] and more evidence is needed to determine effective treatments for screen-detected DM. However, treatment for IFG and IGT was associated with delayed progression to DM.

References

1. Norris SL, Kansagara D, Bougatsos C, et al. Screening for Type 2 Diabetes: Update of 2003 Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 61. AHRQ Publication No. 08-05116-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality. June 2008. 2008. Availible at: http://www.uspreventiveservicestaskforce.org/uspstf08/type2/type2es.pdf. Accessed August 20, 2014.
2. Norris SL, Kansagara D, Bougatsos C, et al. Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(11):855-68.
3. U.S. Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;148(11):846-54.
4. Diabetes Prevention Program Research Group, Knowler WC, Barrett-Connor E, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New Engl J Med. 2002;346(6):393-403.
5. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005;67(2):152-62.
6. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343-50.
7. Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97.
8. Watanabe M, Yamaoka K, Yokotsuka M, et al. Randomized controlled trial of a new dietary education program to prevent type 2 diabetes in a high-risk group of Japanese male workers. Diabetes Care. 2003;26(12):3209-14.
9. Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. Diabetes Care. 2001;24(4):619-24.
10. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537-44.
11. Dyson PA, Hanmmersley MS, Morris RJ, et al. The Fasting Hyperglycaemia Study: II. Randomized controlled trial of reinforced healthy-living advice in subjects with increased but not diabetic fasting plasma glucose. Metabolism. 1997;46(12 Suppl 1):50-5.
12. STOP-NIDDM Trial Research Group, Chiasson JL, Josse RG, et al. Acarbose for the prevention of type 2 diabettes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359(9323):2072-7.
13. Diabetes Prevention Program Research Group, Ratner R, Goldberg R, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Diabetes Care. 2005;28(4):888-94.
14. DREAM Trial Investigators, Bosch J, Yusuf S, et al. Effect of ramipril on the incidence of diabetes. New Engl J Med. 2006;355(15):1551-62.

15. DREAM Trial Investigators, Gerstein HC, Yusuf S, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368(9541):1096-105.
16. American Diabetes Association. Standards of medical care in diabetes - 2014. Diabetes Care. 2014;37(Supplement 1):S14-S80.
17. Centers for Disease Control and Prevention. National diabetes statistics report, 2014. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/diabetes/pubs/factsheet11.htm. Accessed August 20, 2014.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012;35:S64-S71.
19. Centers for Disease Control and Prevention. Diagnosed diabetes by race/ethnicity, sex, and age, 2010. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/menuage.htm. Accessed August 20, 2014.
20. Schiller JS, Lucas JW, Ward BW, et al. Summary health statistics for U.S. adults: National Health Interview Survey, 2010. National Center for Health Statistics. Vital Health Stat 10 (252). 2012. Availible at: http://www.cdc.gov/nchs/data/series/sr_10/sr10_252.pdf Accessed January 30, 2013.
21. Centers for Disease C, Prevention. Increasing prevalence of diagnosed diabetes--United States and Puerto Rico, 1995-2010. MMWR Morb Mortal Wkly Rep. 2012;61(45):918-21.
22. Centers for Disease Control and Prevention. Age-adjusted incidence of end-stage renal disease related to diabetes mellitus (ESRD-DM) per 100,000 diabetic population, by race, ethnicity, and sex, United States, 1980-2008. Available at: http://www.cdc.gov/diabetes/statistics/esrd/fig5.htm Accessed January 30, 2013.
23. Centers for Disease Control and Prevention. Age-adjusted hospital discharge rates for nontraumatic lower extremity amputation per 1,000 diabetic population, by race, United States, 1988-2009. Available at: http://www.cdc.gov/diabetes/statistics/lea/fig6.htm Accessed January 30, 2013.
24. Centers for Disease Control and Prevention. Age-adjusted percentage of people with diabetes aged 35 years or older reporting heart disease or stroke, by race/ethnicity, United States, 1997-2011. Available at: http://www.cdc.gov/diabetes/statistics/cvd/fig6.htm Accessed January 30, 2013.
25. Kochanek KD, Xu J, Murphy SL, et al. Deaths: final data for 2009. Natl Vital Stat Rep. 2011;60(3).
26. Harris MI, Eastman RC. Early detection of undiagnosed diabetes mellitus: a US perspective. Diabetes Metab Res Rev. 2000;16(4):230-6.
27. Harris MI, Klein R, Welborn TA, et al. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care. 1992;15(7):815-9.
28. Crawford AG, Cote C, Couto J, et al. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia and hypertension in the United States: findings from the GE Centricity Electronic Medical Record Database. Popul Health Manag. 2010;13(3):151-61.
29. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. JAMA. 2008;300(24):2886-97.
30. Harder T, Rodekamp E, Schellong K, et al. Birth weight and subsequent risk of type 2

diabetes: a meta-analysis. Am J Epidemiol. 2007;165(8):849-57.
31. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care. 2009;32(2):287-94.
32. Willi C, Bodenmann P, Ghali WA, et al. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007;298(22):2654-64.
33. Parillo M, Riccardi G. Diet composition and the risk of type 2 diabetes: epidemiological and clinical evidence. Br J Nutr. 2004;92(1):7-19.
34. American Diabetes Association. Standards of Medical Care in Diabetes: Position Statement. Diabetes Care. 2013;36(Suppl 1):S11-66.
35. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization. Available at: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Accessed 24 January, 2014.
36. Adamska E, Waszczeniuk M, Goscik J, et al. The usefulness of glycated hemoglobin A1c (HbA1c) for identifying dysglycemic states in individuals without previously diagnosed diabetes. Adv Med Sci. 2012;57(2):296-301.
37. Soulimane S, Simon D, Shaw J, et al. HbA1c, fasting plasma glucose and the prediction of diabetes: Inter99, AusDiab and D.E.S.I.R. Diabetes Res Clin Pract. 2012;96(3):392-9.
38. Tankova T, Chakarova N, Dakovska L, et al. Assessment of HbA1c as a diagnostic tool in diabetes and prediabetes. Acta Diabetol. 2012;49(5):371-8.
39. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011;17 Suppl 2:1-53.
40. American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. 2012. Availible at: http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/CPS/rcps08-2005.Par.0001.File.tmp/October2012SCPS.pdf. Accessed November 30, 2012.
41. Colagiuri S, Davies D, Girgis S, et al. National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di17-diabetes-detection-diagnosis.pdf. Accessed November 30, 2012.
42. Diabetes UK. Early Identification of people with and at high risk of type 2 diabetes and interventions for those at high risk. Available at: http://www.diabetes.org.uk/Documents/Position%20statements/Early%20identification%20of%20Type%202%20diabetes%20Position%20statement.pdf. Accessed November 30, 2012.
43. Canadian Task Force on Preventive Health Care. Recommendations on screening for type 2 diabetes in adults. CMAJ. 2012;184(15):1687-96.
44. World Health Organization. Screening for type 2 diabetes. Report of a World Health Organization and International Diabetes Federation meeting. Available at: http://www.who.int/diabetes/publications/en/screening_mnc03.pdf. Accessed Nov 30, 2012.
45. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF. Rockville (MD);July 2008. Availible at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm Accessed January 30, 2013.

46. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160(4):267-70.
47. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. Br Med J. 2003;327(7414):557-60.
48. Lindeman RD, Yau CL, Baumgartner RN, et al. Longitudinal study of fasting serum glucose concentrations in healthy elderly. The New Mexico Aging Process Study. J Nutr Health Aging. 2003;7(3):172-7.
49. Simmons RK, Rahman M, Jakes RW, et al. Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. Diabetologia. 2011;54(2):312-9.
50. Takahashi O, Farmer AJ, Shimbo T, et al. A1C to detect diabetes in healthy adults: when should we recheck? Diabetes Care. 2010;33(9):2016-7.
51. Ogden CL, Fryar CD, Carroll MD, et al. Mean body weight, height and body mass index, United States 1960-2002. Advance data from vital and health statistics; no. 347. Hyattsville, MD: National Center for Health Statistics; 2004. Availible at: http://www.cdc.gov/nchs/data/ad/ad347.pdf.
52. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis.[Erratum appears in Lancet. 2010 Apr 17;375(9723):1346]. Lancet. 2010;375(9723):1365-74.
53. Noble D, Mathur R, Dent T, et al. Risk models and scores for type 2 diabetes: systematic review. BMJ. 2011;343:d7163.
54. Buijsse B, Simmons RK, Griffin SJ, et al. Risk assessment tools for identifying individuals at risk of developing type 2 diabetes. Epidemiol Rev. 2011;33(1):46-62.
55. Mann DM, Bertoni AG, Shimbo D, et al. Comparative validity of 3 diabetes mellitus risk prediction scoring models in a multiethnic US cohort: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2010;171(9):980-8.
56. Abbasi A, Peelen LM, Corpeleijn E, et al. Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. BMJ. 2012;345:e5900.
57. Waugh N, Scotland G, McNamee P, et al. Screening for type 2 diabetes: literature review and economic modelling. Health Technology Assessment (Winchester, England). 2007;11(17):iii-iv, ix-xi, 1-125.
58. CDC Diabetes Cost-Effectiveness Study Group. The cost-effectiveness of screening for type 2 diabetes. JAMA. 1998;280:1757-63.
59. Goyder EC, Irwig LM. Screening for type 2 diabetes mellitus: a decision analytic approach. Diabetic Med. 2000;17:469-77.
60. Hofer TP, Vijan S, Hayward RA. Estimating the microvascular benefits of screening for type 2 diabetes mellitus. Int J Technol Assess Health Care. 2000;16(3):822-33.
61. Chen TH, Yen MF, Tung TH. A computer simulation model for cost-effectiveness analysis of mass screening for type 2 diabetes mellitus. Diabetes Res Clin Pract. 2001;54:S37-42.
62. Hoerger TJ, Harris R, Hicks KA, et al. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. Ann Intern Med. 2004;140:689-99.
63. Glumer C, Yuyun M, Griffin S, et al. What determines the cost-effectiveness of diabetes screening? Diabetologia. 2006;49(7):1536-44.
64. Gillies CL, Lambert PC, Abrams KR, et al. Different strategies for screening and

prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ. 2008;336(7654):1180-5.
65. Hoerger TJ, Hicks KA, Sorensen SW, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007;30(11):2874-9.
66. Mortaz S, Wessman C, Duncan R, et al. Impact of screening and early detection of impaired fasting glucose tolerance adn type 2 diabetes in Canada; a Markov model simulation. Clinicoecon Outcomes Res. 2012;4:91-7.
67. Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. Lancet. 2012;380(9855):1741-8.
68. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial.[Erratum appears in Lancet. 2012 Mar 3;379(9818):804]. Lancet. 2011;378(9786):156-67.
69. Simmons RK, Sharp SJ, Sandbaek A, et al. Does early intensive multifactorial treatment reduce total cardiovascular burden in individuals with screen-detected diabetes? Findings from the ADDITION-Europe cluster-randomized trial. Diabet Med. 2012;29(11):e409-16.
70. Stern M, Williams K, Eddy D, et al. Validation of prediction of diabetes by the Archimedes model and comparison with other predicting models. Diabetes Care. 2008;31(8):1670-1.
71. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165(12):1410-9.
72. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group.[Erratum appears in BMJ 1999 Jan 2;318(7175):29]. BMJ. 1998;317(7160):703-13.
73. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351(9118):1755-62.
74. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med. 1998;338(10):645-52.
75. Schrier RW, Estacio RO, Esler A, et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002;61(3):1086-97.
76. Schrier RW, Estacio RO, Mehler PS, et al. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol. 2007;3(8):428-38.
77. Harris R, Donahue K, Rathore SS, et al. Screening Adults for Type 2 Diabetes: A Review of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003;138(3):215-29.
78. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and

antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial.[Erratum appears in JAMA. 2006 Jun 21;295(23):2726]. JAMA. 2002;288(19):2421-31.
79. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575-85.
80. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370(9590):829-40.
81. Zhang Y, Zhang X, Liu L, et al. Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. Eur Heart J. 2011;32(12):1500-8.
82. Costa J, Borges M, David C, et al. Efficacy of liipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomized controlled trials. BMJ. 2006;332(7550).
83. Cholesterol Treatment Trialists Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25.
84. Tajima N, Kurata H, Nakaya N, et al. Pravastatin reduces the risk for cardiovascular disease in Japanese hypercholesterolemic patients with impaired fasting glucose or diabetes: diabetes subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. Atherosclerosis. 2008;199(2):455-62.
85. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.[Erratum appears in BMJ 2002 Jan 19;324(7330):141]. BMJ. 2002;324(7329):71-86.
86. Sacco M, Pellegrini F, Roncaglioni MC, et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care. 2003;26(12):3264-72.
87. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352(13):1293-304.
88. U.S. Preventive Services Task Force. Aspirin for the Primary Prevention of Cardiovascular Events: Final Research Plan. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/topicsprog.htm. Accessed January 4, 2014.
89. Rahman M, Simmons RK, Hennings SH, et al. How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. Diabetologia. 2012;55(6):1651-9.
90. Lauritzen T, Borch-Johnsen K, Griffin S, et al. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. Int J Obes. 2000;24:S6-S11.
91. Park P, Simmons RK, Prevost AT, et al. Screening for type 2 diabetes is feasible,

acceptable, but associated with increased short-term anxiety: a randomised controlled trial in British general practice. BMC Public Health. 2008;8:350.
92. Rahman M, Simmons RK, Hennings SH, et al. Effect of screening for Type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort. Diabet Med. 2012;29(7):886-92.
93. Paddison CAM, Eborall HC, French DP, et al. Predictors of anxiety and depression among people attending diabetes screening: a prospective cohort study embedded in the ADDITION (Cambridge) randomized control trial. Br J Health Psychol. 2011;16(Pt 1):213-26.
94. Eborall HC, Griffin SJ, Prevost AT, et al. Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. BMJ. 2007;335(7618):486.
95. Andrews RC, Cooper AR, Montgomery AA, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet. 2011;378(9786):129-39.
96. Davies MJ, Heller S, Skinner TC, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial.[Erratum appears in BMJ. 2008 Apr 19;336(7649):doi:10.1136/bmj.39553.528299.AD]. BMJ. 2008;336(7642):491-5.
97. Khunti K, Gray LJ, Skinner T, et al. Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ. 2012;344:e2333.
98. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance.[Erratum appears in N Engl J Med. 2011 Jul 14;365(2):189], [Erratum appears in N Engl J Med. 2011 Sep 1;365(9):869]. N Engl J Med. 2011;364(12):1104-15.
99. Dream Trial Investigators, Dagenais GR, Gerstein HC, et al. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care. 2008;31(5):1007-14.
100. Florez H, Pan Q, Ackermann RT, et al. Impact of lifestyle intervention and metformin on health-related quality of life: the diabetes prevention program randomized trial. J Gen Intern Med. 2012;27(12):1594-601.
101. Kawamori R, Tajima N, Iwamoto Y, et al. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet. 2009;373(9675):1607-14.
102. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet. 2008;371(9626):1783-9.
103. Navigator Study Group, Holman RR, Haffner SM, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events.[Erratum appears in N Engl J Med. 2010 May 6;362(18):1748]. N Engl J Med. 2010;362(16):1463-76.
104. Navigator Study Group, McMurray JJ, Holman RR, et al. Effect of valsartan on the

incidence of diabetes and cardiovascular events.[Erratum appears in N Engl J Med. 2010 May 6;362(18):1748]. N Engl J Med. 2010;362(16):1477-90.
105. Nijpels G, Boorsma W, Dekker JM, et al. A study of the effects of acarbose on glucose metabolism in patients predisposed to developing diabetes: the Dutch acarbose intervention study in persons with impaired glucose tolerance (DAISI). Diabetes Metab Res Rev. 2008;24(8):611-6.
106. Ramachandran A, Snehalatha C, Mary S, et al. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009;52(6):1019-26.
107. Saito T, Watanabe M, Nishida J, et al. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171(15):1352-60.
108. Uusitupa M, Peltonen M, Lindström J, et al. Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study—secondary analysis of the randomized trial. PLoS ONE [Electronic Resource]. 2009;4(5):e5656.
109. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet. 2010;376(9735):103-11.
110. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2(6):474-80.
111. Chiasson J-L, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. The Lancet. 2002;359(9323):2072-7.
112. Chiasson J, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The stop-niddm trial. JAMA. 2003;290(4):486-94.
113. Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. Arch Intern Med. 2000;160(9):1321.
114. Buehler AM, Cavalcanti AB, Berwanger O, et al. Effect of tight blood glucose control versus conventional control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther. 2013;31(3):147-60.
115. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2012(2).
116. Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med. 2012;172(10):761-9.
117. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ. 2011;343:d6898.
118. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169.

119. Castagno D, Baird-Gunning J, Jhund PS, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. Am Heart J. 2011;162(5):938-48.e2.
120. Wu H, Xu M-j, Zou D-j, et al. Intensive glycemic control and macrovascular events in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Chin Med J (Engl). 2010;123(20):2908-13.
121. Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med. 2009;151(6):394-403.
122. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765-72.
123. Ma J, Yang W, Fang N, et al. The association between intensive glycemic control and vascular complications in type 2 diabetes mellitus: a meta-analysis. Nutr Metab Cardiovasc Dis. 2009;19(9):596-603.
124. Mannucci E, Monami M, Lamanna C, et al. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2009;19(9):604-12.
125. Bangalore S, Kumar S, Lobach I, et al. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. Circulation. 2011;123(24):2799-810, 9 p following 810.
126. Poulter NR. Blood pressure and glucose control in subjects with diabetes: new analyses from ADVANCE. Journal of Hypertension - Supplement. 2009;27(1):S3-8.
127. ACCORD Study group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.
128. ACCORD Study Group, Gerstein HC, Miller ME, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364(9):818-28.
129. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus.[Erratum appears in N Engl J Med. 2010 May 6;362(18):1748]. N Engl J Med. 2010;362(17):1563-74.
130. Zoungas S, de Galan BE, Ninomiya T, et al. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care. 2009;32(11):2068-74.
131. Gaede P, Lund-Andersen H, Parving H-H, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.
132. De Berardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009;339:b4531.
133. Stavrakis S, Stoner JA, Azar M, et al. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. Am J Med Sci. 2011;341(1):1-9.
134. Reboldi G, Gentile G, Angeli F, et al. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens. 2011;29(7):1253-69.
135. Charles M, Ejskjaer N, Witte DR, et al. Prevalence of neuropathy and peripheral arterial

disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care. 2011;34(10):2244-9.
136. van den Donk M, Gorter KJ, Rutten GE. No negative effects of a multi-factorial, intensified treatment on self-reported health status, treatment satisfaction, and diabetes-related distress in screen-detected type 2 diabetes patients. The ADDITION-Netherlands study. Qual Life Res. 2010;19(4):509-13.
137. Janssen PG, Gorter KJ, Stolk RP, et al. Randomised controlled trial of intensive multifactorial treatment for cardiovascular risk in patients with screen-detected type 2 diabetes: 1-year data from the ADDITION Netherlands study. Br J Gen Pract. 2009;59(558):43-8.
138. van den Donk M, Griffin SJ, Stellato RK, et al. Effect of early intensive multifactorial therapy compared with routine care on self-reported health status, general well-being, diabetes-specific quality of life and treatment satisfaction in screen-detected type 2 diabetes mellitus patients (ADDITION-Europe): a cluster-randomised trial. Diabetologia. 2013;56:2367-77.
139. Schwartz AV, Margolis KL, Sellmeyer DE, et al. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes Care. 2012;35(7):1525-31.
140. Ismail-Beigi F, Craven TE, O'Connor PJ, et al. Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. Kidney Int. 2012;81(6):586-94.
141. O'Connor PJ, Narayan KMV, Anderson R, et al. Effect of intensive versus standard blood pressure control on depression and health-related quality of life in type 2 diabetes: the ACCORD trial. Diabetes Care. 2012;35(7):1479-81.
142. Sullivan MD, Anderson RT, Aron D, et al. Health-related quality of life and cost-effectiveness components of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: rationale and design. Am J Cardiol. 2007;99(12A):90i-102i.
143. ACCORD Study Group, Group AES, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes.[Erratum appears in N Engl J Med. 2011 Jan 13;364(2):190]. N Engl J Med. 2010;363(3):233-44.
144. Anderson RT, Narayan KMV, Feeney P, et al. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care. 2011;34(4):807-12.
145. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol. 2009;20(4):883-92.
146. Stefansdottir G, Zoungas S, Chalmers J, et al. Intensive glucose control and risk of cancer in patients with type 2 diabetes. Diabetologia. 2011;54(7):1608-14.
147. Beulens JW, Patel A, Vingerling JR, et al. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. Diabetologia. 2009;52(10):2027-36.
148. Araki A, Iimuro S, Sakurai T, et al. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial--study design, baseline characteristics and effects of intervention. Geriatr Gerontol Int. 2012;12 Suppl 1:7-17.
149. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of

atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.[Erratum appears in JAMA. 2009 May 13;301(18):1882]. JAMA. 2008;300(18):2134-41.
150. Okada S, Morimoto T, Ogawa H, et al. Differential effect of low-dose aspirin for primary prevention of atherosclerotic events in diabetes management: a subanalysis of the JPAD trial. Diabetes Care. 2011;34(6):1277-83.
151. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155-63.
152. Howard BV, Roman MJ, Devereux RB, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA. 2008;299(14):1678-89.
153. Gæde P, Vedel P, Larsen N, et al. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. N Engl J Med. 2003;348(5):383-93.
154. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.
155. Holman RR, Paul SK, Bethel MA, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359(15):1565-76.
156. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1028], [Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1024-5; PMID: 19726779]. N Engl J Med. 2009;360(2):129-39.
157. Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. Am Heart J. 2006;152(1):27-38.
158. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group.[Erratum appears in Lancet 1999 Aug 14;354(9178):602]. Lancet. 1999;352(9131):837-53.
159. Service FJ, Daube JR, O'Brien PC, et al. Effect of blood glucose control on peripheral nerve function in diabetic patients. Mayo Clin Proc. 1983;58(5):283-9.
160. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970;19:Suppl:789-830.
161. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. Diabetologia. 2011;54(1):25-31.
162. Reboldi G, Gentile G, Manfreda VM, et al. Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes. Curr Cardiol Rep. 2012;14(1):89-96.
163. Lv J, Perkovic V. Blood pressure management in diabetes: a path forward? J Hypertens. 2011;29(7):1283-4.
164. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840.

165. Armato J, DeFronzo RA, Abdul-Ghani M, et al. Successful treatment of prediabetes in clinical practice: targeting insulin resistance and -cell dysfunction. Endocr Pract. 2012;18(3):342-50.
166. Lu Y-H, Lu J-M, Wang S-Y, et al. Outcome of intensive integrated intervention in participants with impaired glucose regulation in China. Adv Ther. 2011;28(6):511-9.
167. Rasmussen SS, Glumer C, Sandbaek A, et al. General effect on high-risk persons when general practitioners are trained in intensive treatment of type 2 diabetes. Scand J Prim Health Care. 2008;26(3):166-73.
168. Lindblad U, Lindberg G, Månsson NO, et al. Can sulphonylurea addition to lifestyle changes help to delay diabetes development in subjects with impaired fasting glucose? The Nepi ANtidiabetes StudY (NANSY). Diabetes Obes Metab. 2011;13(2):185-8.
169. Penn L, White M, Oldroyd J, et al. Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK. BMC Public Health. 2009;9:342.
170. Sakane N, Sato J, Tsushita K, et al. Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health. 2011;11(1):40.
171. Lindahl B, Nilssön TK, Borch-Johnsen K, et al. A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: Pronounced short-term impact but long-term adherence problems. Scand J Public Health. 2009;37(4):434-42.
172. Katula JA, Vitolins MZ, Morgan TM, et al. The Healthy Living Partnerships to Prevent Diabetes study: 2-year outcomes of a randomized controlled trial. Am J Prev Med. 2013;44(4 Suppl 4):S324-32.
173. Pan C-Y, Gao Y, Chen J-W, et al. Efficacy of acarbose in Chinese subjects with impaired glucose tolerance. Diabetes Res Clin Pract. 2003;61(3):183-90.
174. Calles-Escandon J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33(4):721-7.
175. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010(4).
176. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-44.
177. Grarup N, Rose CS, Andersson EA, et al. Studies of association of variants near the HHEX, CDKN2A/B, and IGF2BP2 genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. Diabetes. 2007;56(12):3105-11.
178. Sparso T, Andersen G, Nielsen T, et al. The GCKR rs780094 polymorphism is associated with elevated fasting serum triacylglycerol, reduced fasting and OGTT-related insulinaemia, and reduced risk of type 2 diabetes.[Erratum appears in Diabetologia. 2008 Feb;51(2):383]. Diabetologia. 2008;51(1):70-5.
179. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012;35(4):731-7.

Figure 1. Analytic Framework

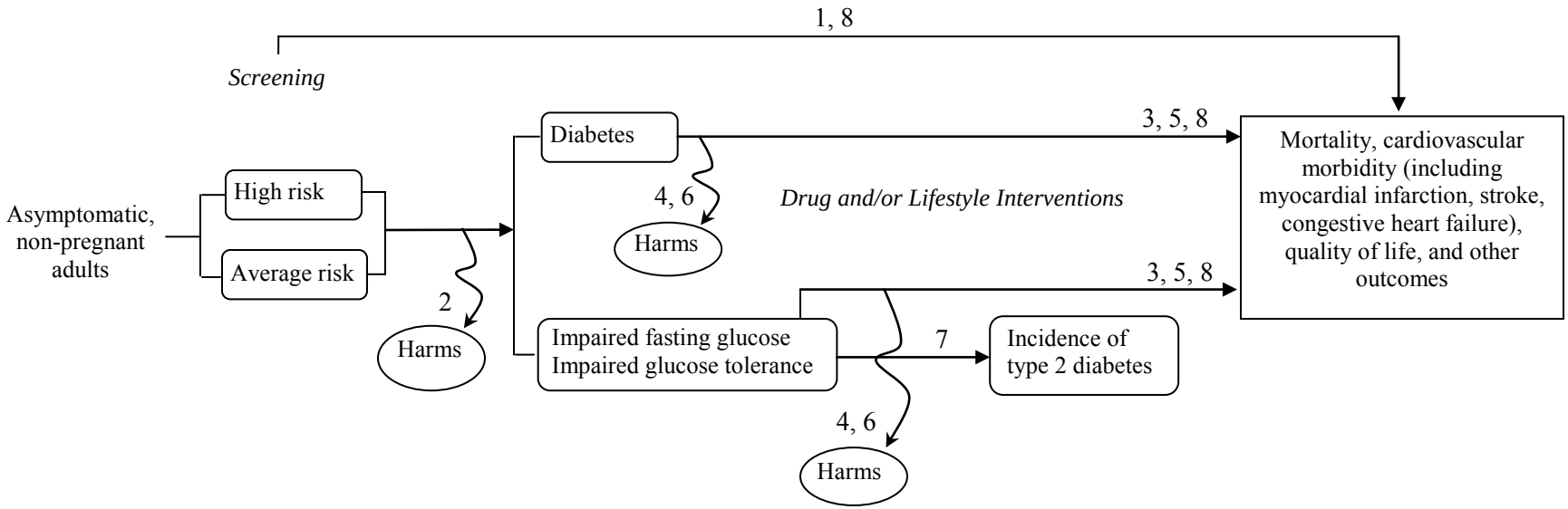
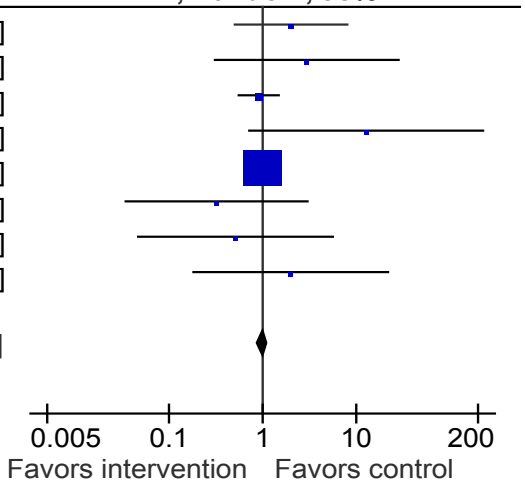


Figure 2. Meta-Analysis of the Effect of Glucose-Lowering Drugs on All-Cause Mortality in Persons With Screen-Detected and Early DM, IFG, or IGT

	Intervention		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chiasson, 2002*	6	682	3	686	1.1%	2.01 [0.51, 8.01]	
DeFronzo, 2011	3	303	1	299	0.4%	2.96 [0.31, 28.30]	
DREAM, 2006*	30	2635	33	2634	8.5%	0.91 [0.56, 1.49]	
Kawamori, 2009	6	897	0	881	0.2%	12.77 [0.72, 226.31]	
NAVIGATOR, 2010	310	4645	312	4661	88.7%	1.00 [0.86, 1.16]	
Nijpels, 2008	1	60	3	58	0.4%	0.32 [0.03, 3.01]	
Ramachandran, 2006*	1	262	2	269	0.4%	0.51 [0.05, 5.63]	
Ramachandran, 2009	2	203	1	203	0.4%	2.00 [0.18, 21.88]	
Total (95% CI)		**9687**		**9691**	**100.0%**	**1.00 [0.87, 1.16]**	
Total events	359		355				

Heterogeneity: Tau² = 0.00; Chi² = 6.66, df = 7 (P = 0.46); I² = 0%

Test for overall effect: Z = 0.04 (P = 0.97)



*From prior report

Figure 3. Meta-Analysis of the Effect of Glucose-Lowering Drugs on Cardiovascular Mortality in Persons With Screen-Detected and Early DM, IFG, or IGT

	Intervention		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Chiasson, 2002*	1	682	2	686	1.0%	0.50 [0.05, 5.53]	
DPP, 2002*	1	1073	4	1082	1.1%	0.25 [0.03, 2.25]	
DREAM, 2006*	12	2635	10	2634	7.8%	1.20 [0.52, 2.77]	
NAVIGATOR, 2010	126	4645	118	4661	89.5%	1.07 [0.84, 1.37]	
Ramachandran, 2009	2	204	0	203	0.6%	4.98 [0.24, 103.00]	
Total (95% CI)		**9239**		**9266**	**100.0%**	**1.07 [0.84, 1.35]**	
Total events	142		134				

Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 4 (P = 0.54); I² = 0%

Test for overall effect: Z = 0.53 (P = 0.60)

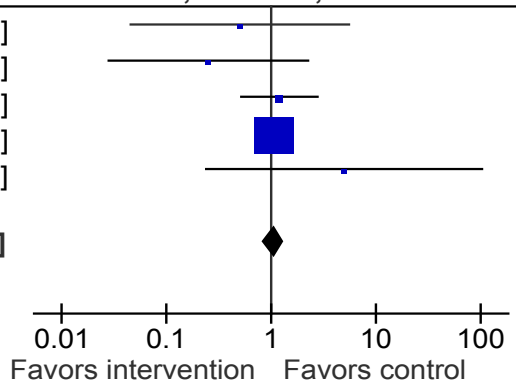


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Figure 4. Meta-Analysis of the Effect of Lifestyle Interventions on Incidence of Progression to DM

Study or Subgroup	Intensive lifestyle Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
DPP, 2002*	155	1079	313	1082	15.0%	0.50 [0.42, 0.59]
Katula, 2013	4	151	11	150	5.1%	0.36 [0.12, 1.11]
Kosaka, 2005*	3	102	33	356	4.9%	0.32 [0.10, 1.01]
Li, 2014	312	430	124	138	15.6%	0.81 [0.74, 0.88]
Lindahl, 2009	5	83	20	85	6.5%	0.26 [0.10, 0.65]
Penn, 2009	5	51	11	51	6.1%	0.45 [0.17, 1.22]
Ramachandran, 2006*	47	120	73	133	14.1%	0.71 [0.54, 0.94]
Saito, 2011	35	330	51	311	12.5%	0.65 [0.43, 0.97]
Sakane, 2011	9	146	18	150	8.0%	0.51 [0.24, 1.11]
Tuomilehto, 2001*	27	265	59	257	12.2%	0.44 [0.29, 0.68]
Total (95% CI)		**2757**		**2713**	**100.0%**	**0.53 [0.39, 0.72]**
Total events	602		713			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 72.10$, df = 9 ($P < 0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 4.03$ ($P < 0.0001$)

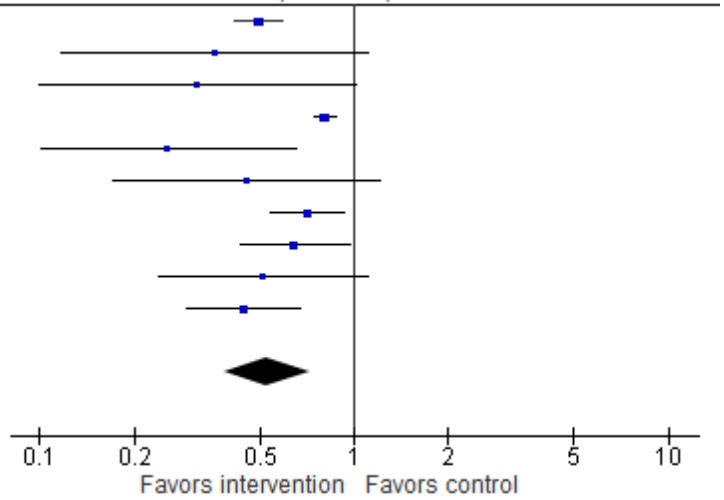

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Figure 5. Meta-Analysis of the Effect of Thiazolidinediones on Incidence of Progression to DM

Study or Subgroup	TZDs Events	TZDs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
DeFronzo, 2011	15	303	50	299	28.6%	0.30 [0.17, 0.52]
DREAM, 2006*	280	2635	658	2634	37.0%	0.43 [0.37, 0.48]
Ramachandran, 2009	54	181	59	186	34.3%	0.94 [0.69, 1.28]
Total (95% CI)		**3119**		**3119**	**100.0%**	**0.50 [0.27, 0.92]**
Total events	349		767			

Heterogeneity: Tau² = 0.25; Chi² = 24.78, df = 2 (P < 0.00001); I² = 92%

Test for overall effect: Z = 2.22 (P = 0.03)

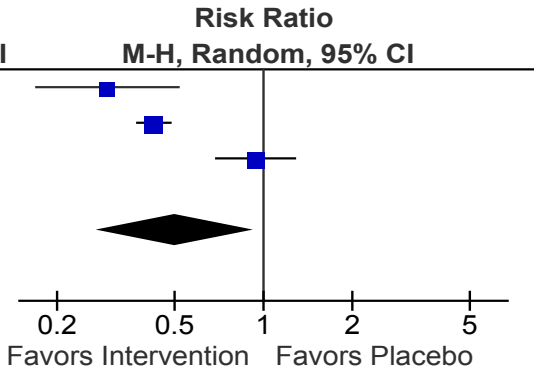

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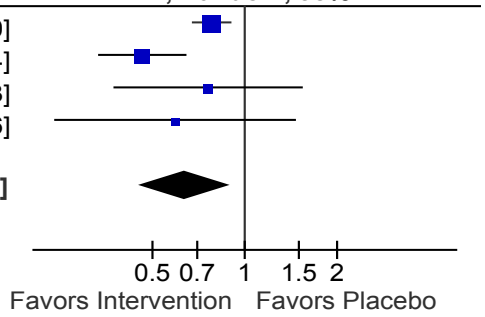
Figure 6. Meta-Analysis of the Effect of Alpha-Glucosidase Inhibitors on Incidence of Progression to DM

Study or Subgroup	a-Glucosidase Inhibitors Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chiasson, 2002*	221	682	285	686	41.2%	0.78 [0.68, 0.90]
Kawamori, 2009	50	897	106	881	31.9%	0.46 [0.34, 0.64]
Nijpels, 2008	11	60	14	58	15.7%	0.76 [0.38, 1.53]
Pan, 2003*	7	125	12	127	11.2%	0.59 [0.24, 1.46]
Total (95% CI)		**1764**		**1752**	**100.0%**	**0.64 [0.45, 0.90]**
Total events	289		417			

Heterogeneity: Tau² = 0.07; Chi² = 8.89, df = 3 (P = 0.03); I² = 66%

Test for overall effect: Z = 2.54 (P = 0.01)



*From prior report

Table 1. Test Values for Normal, IFG, or IGT and Type 2 Diabetes Definitions

Test	Normal	IFG or IGT	Type 2 Diabetes
Hemoglobin a1c	<5.7%	5.7 to 6.4%	>6.5% on 2 separate tests
Random plasma glucose	<140 mg/dL	140 to 199 mg/dL	>200 mg/dL (suggestive)
Fasting plasma glucose	<100 mg/dL	100 to 125 mg/dL	>126 mg/dL
OGTT after 2 hours	<140 mg/dL	140 to 199 mg/dL	>200 mg/dL

Abbreviations: IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

Table 2. Prevalence of Diagnosed Diabetes in the United States

Race/Ethnicity	Sex	Ages 0-44	Ages 45-64	Ages 65-74	Ages 75+	Age-Adjusted
White	Males	1.5%	12.4%	22.8%	21.7%	6.8%
White	Females	1.5%	10.0%	18.4%	16.6%	5.4%
Black	Males	2.5%	17.6%	30.7%	38.1%	9.9%
Black	Females	2.4%	17.1%	31.2%	25.9%	9.0%
Asian	Males	1.4%	12.7%	34.4%	30.4%	7.8%
Asian	Females	1.0%	11.3%	18.3%	18.7%	5.5%
Hispanic	Males	1.8%	16.7%	29.1%	41.1%	9.3%
Hispanic	Females	1.6%	19.0%	31.6%	31.4%	9.3%
Native Pacific Islanders	-					23.7%*
American Indians/Alaska Natives	-					16.3%

*Standard error >30% and ≤50%; estimate should be interpreted with caution as it does not meet standards of reliability or precision.

Table 3. Characteristics of Seven Risk Models or Scores With Potential for Use in Clinical Practice

Score/Model	Risk Factors	Development		External Validation	
		Country	AUROC	Country	AUROC
ARIC	Age, ethnicity, waist circumference, height, systolic BP, family history of diabetes, FG, TG, HDL-c	Germany	0.80	USA	0.84
Ausdrisk	Age, sex, ethnicity, parental history of diabetes, history of high blood glucose, use of BP medication, smoking, physical inactivity, waist circumference	Australia	0.78	NA	NA
Cambridge Risk Score	Age, sex, use of steroids, use of BP medication, family history of diabetes, BMI, smoking	UK	0.74[a]	UK	0.72
FINDRISC	Age, BMI, waist circumference, use of BP medication, history of high blood glucose, physical inactivity, daily consumption of vegetables, fruits, and berries	Finland	0.85	Holland, Denmark, Sweden, UK, Australia[b]	0.76
Framingham Offspring	FG, BMI, HDL-c, parental history of diabetes, TG, BP	USA	0.85	USA	0.78
San Antonio	Age, sex, ethnicity, FG, systolic BP, HDL-c, BMI, family history of diabetes in first degree relative	USA	0.84	USA[c]	0.83
QDScore	Age, sex, ethnicity, BMI, smoking, family history of diabetes, Townsend deprivation score, CVD, use of steroids	UK	0.83 men, 0.85 women	UK	0.80 men, 0.81 women

[a]Threshold = 0.38.
[b]Validation used modification of risk factors from original score or didn't state exact factors used.
[c]Also validated in Iran and UK.

Abbreviations: ARIC = Atherosclerosis Risk in Communities; AUROC = area under the receiver operating curve; BMI = body mass index: BP = blood pressure; CVD = cardiovascular disease; FG = fasting plasma glucose; FINDRISC = Finnish Diabetes Risk Score; NA = not available; HDL-c = high density lipoprotein cholesterol; TG = triglycerides; UK = United Kingdom; USA = United States of America.

Source: Adapted from Noble 2011.[53]

Table 4. Studies Modeling Screening for DM Published Since the Previous USPSTF Report

Author, Year Country	Screening Details	Type of Model	Assumptions Regarding Treatment Benefits	Cost Effectiveness Outcomes	Length of Followup	Calibrated?	Comments
Gillies, 2008[64] UK	1. Screening for **diabetes** 2. Screening **for IGT or diabetes**, followed by **lifestyle** intervention 3. Screening for **IGT or diabetes,** followed by **pharmacologica**l interventions 4. No screening Start screening at age 45	Hybrid: decision tree + Markov model	Intervention effects on risk of developing diabetes for: Lifestyle vs standard treatment: HR -0.65 Drugs vs placebo: HR -0.43 Mortality rates: 0.32 to 15.68 (increases with age) per 100 person years Increased risk of death with diabetes: HR 0.76 Increased risk of death for 1% increase in HbA1c: HR 0.104	ICER compared with no screening: Screening for diabetes (no intervention for patients with IGT): £14,150 ($27,860)/QALY Screening for diabetes and IGT followed by lifestyle interventions: £6,242 ($12,290)/QALY Screening for diabetes and IGT followed by pharmacological interventions: £7,023 ($13,828)/QALY	50 years	No	Needed to run model for at least 30 years for cost effectiveness
Hoerger, 2007[65] US	1. Screening overweight and obese subjects (BMI ≥25) followed by DPP lifestyle intervention for those with **both** IGT and IFG 2. Same as A except for those with **either** IGT or IFG or both 3. No screening and no treatment Population 45 to 74 years of age at screening	Markov model	DPP lifestyle intervention reduction in risk for onset of diabetes 55.3% Effect of diabetes on clinical outcomes NR	ICER compared with no screening: Strategy 1: $8,181 per QALY Strategy 2: $9,511 per QALY	Lifetime	No	DPP = lifestyle modification program with goals of 7% weight loss and 150 minutes of weekly physical activity
Kahn, 2010[52] US	1. Start screening at age **30** years and repeat every **3** years 2. Start screening at age **45** years and repeat **every year** 3. Start screening at age **45** years and repeat every **3** years 4. Start screening at age **45** years and repeat every **5** years 5. Start screening at age **60** years and repeat every **3** years 6. Start screening when BP **>140/90** mmHg and repeat **every year** 7. Start screening when BP **>135/80** mmHg and repeat	Archimedes	Model calibrated with effects of metformin and lifestyle modification in the DPP study and effects of atorvastatin on cardiovascular risk in the CARDS trial (underestimated effect of atorvastatin on stroke, but modified to account for these effects)	ICER compared with no screening: Age 30 years, every 3 years: $10,512/QALY Age 45 years, every year: $15,509/QALY Age 45 years, every 3 years: $9,731/QALY Age 45 years, every 5 years: $9,786/QALY Age 60 years, every 3 years: $25,738/QALY Hypertension diagnosis, every year: $6,287/QALY Hypertension diagnosis, every 5 years: $6,490/QALY Age 30 years, every 6 months (max):	50 years	Model validated for incidence of type 2 diabetes melitus and rate of hyper-glycemia progression	Time and biological variables are continuous and the interaction of variables preserved with the Archimedes model compared to the Markov model

Table 4. Studies Modeling Screening for DM Published Since the Previous USPSTF Report

Author, Year Country	Screening Details	Type of Model	Assumptions Regarding Treatment Benefits	Cost Effectiveness Outcomes	Length of Followup	Calibrated?	Comments
	every **5** years 8. Start screening at age **30** years and repeat every 6 months (max screening) 9. No screening			$40,778/QALY			
Mortaz, 2012[66] Canada	1.Screening for prediabetes and diabetes every 3 years 2. Screening for prediabetes and diabetes every 5 years 3. If patient has prediabetes, then annual screening 4. No screening Start screening at age 40	Markov model	DPP lifestyle intervention reduction in incidence of diabetes by 58% Effect of diabetes on clinical outcomes NR	Costs/QALY with screening: Once every 3 years: $2,281 Once every 5 years: $2,116 Annually: $2,367 Costs for each QALY with no screening: $2,890	10 years	No	DPP = lifestyle modification program with goals of 7% weight loss and 150 minutes of weekly physical activity

Abbreviations: BMI = body mass index; BP = blood pressure; CARDS = Collaborative Atorvastatin Diabetes Study; DPP = Diabetes Prevention Program; HR = hazard ratio; ICER = incremental cost-effectiveness ratios; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NR = not reported; QALY = quality adjusted life year.

Table 5. More Versus Less Intensive Blood Pressure Control in Persons With and Without DM

2005 Meta-Analysis of Five Trials

	Intensive vs. Standard Blood Pressure Lowering (mean achieved BP 139/81 vs. 143/84 mm Hg) Relative Risk; 95% CI			
	All-Cause Mortality	**Cardiovascular Mortality**	**Stroke**	**Cardiovascular Events[a]**
DM	10% (179/1731) vs 10% (184/1868); 0.73; 0.56 to 0.95	6% (106/1731) vs 6% (120/1868); 0.67; 0.40 to 1.12	4% (63/1731) vs 5% (86/1868); 0.64; 0.46 to 0.89	14% (236/1731) vs 14% (262/1868); 0.75; 0.61 to 0.94
No DM	4% (225/6303) vs 3% (365/12080); 1.07; 0.80 to 1.42	2% (105/6303) vs 1% (149/12080); 1.30; 1.01 to 1.66	2% (103/6303) vs 2% (204/12080); 0.89; 0.70 to 1.13	4% (266/6303) vs 4% (460/12080); 1.01; 0.87 to 1.17

Hypertension Optimal Treatment (HOT) Trial[73]

	Intensive vs. Standard Blood Pressure Lowering[b] (mean achieved BP 140/81 vs. 143/84 mm Hg) Relative Risk; 95% CI			
	All-Cause Mortality	**Cardiovascular Mortality**	**Stroke**	**Cardiovascular Events[c]**
DM	3% (17/499) vs 6% (59/1002); 0.58; 0.34 to 0.98	1% (7/499) vs 4% (42/1002); 0.33; 0.15 to 0.74	3% (12/499) vs 3% (30/1002); 0.80; 0.41 to 1.56	6% (30/499) vs 9% (90/1002); 0.67; 0.45 to 1.00
No DM	3% (190/5763) vs 3% (323/11526); 1.18; 0.99 to 1.40	2% (89/5763) vs 1% (135/11526); 1.32; 1.01 to 1.72	1% (77/5763) vs 2% (175/11526); 0.88; 0.67 to 1.15	4% (233/5763) vs 4% (460/11526); 1.01; 0.87 to 1.18

Felodipine Event Reduction (FEVER) Trial[81]

	Intensive vs. Standard Blood Pressure Lowering (mean achieved BP 138/82 vs. 142/84 mm Hg) Hazard Ratio; 95% CI[d]			
	All-Cause Mortality	**Cardiovascular Mortality**	**Stroke**	**Cardiovascular Events[c]**
DM	1.00; 0.56 to 1.77	1.01; 0.5 to 1.99	0.56; 0.34 to 0.92	0.80; 0.54 to 1.17
No DM	0.64; 0.48 to 0.84	0.64; 0.45 to 0.92	0.77; 0.62 to 0.96	0.71; 0.59 to 0.86

[a]Cardiovascular events = CV mortality, stroke, CHD events, and heart failure.
[b]Intensive = DBP <80 mm HG; Standard = DBP ≤85 or 90 mm Hg.
[c]Cardiovascular events = CV mortality, nonfatal MI, nonfatal stroke.
[d]n/N not reported.
[e]Cardiovascular events = CV mortality, non-fatal stroke, non-fatal MI, aortic aneurysm, heart failure, coronary angioplasty or CABG, peripheral vascular disease requiring surgery.

Table 6. Effect of Screening for DM on Health Outcomes

Author, Year Study Name Quality	Study Design Setting Country	Interventions	Population	Duration of Followup	Results
Simmons 2012[67] ADDITION-Cambridge Good	Cluster RCT 33 general practices United Kingdom	A. Invited to stepwise screening of high-risk participants with random capillary blood glucose and HbA1c (n=15,089; 27 sites) A1. Invited to and attended screening (n=11,737/15,089; 78%) A2. Did not attend screening (n=3,352/15,089; 22%) B. No screening (n=4,137; 5 sites)	A vs B Mean age 58 vs 58 years 64% vs 64% male Race not reported Mean BMI 30.6 vs 30.5 kg/m^2 Median diabetes risk score 0.34 vs 0.35[a] Index of Multiple Deprivation score: 12.9 (SD 7.7) vs 16.1 (SD 9.0)[b]	10 years	A vs B All-cause mortality: HR 1.06 (95% CI 0.90 to 1.25) Cardiovascular mortality: HR 1.02 (95% CI 0.75 to 1.38) Cancer mortality: HR 1.08 (95% CI 0.90 to 1.30) Diabetes-related mortality: HR 1.26 (95% CI 0.75 to 2.10) Other mortality: HR 1.10 (95% CI 0.87 to 1.39) A1 vs A2 All-cause mortality: HR 2.01, 95% CI 1.74 to 2.32
Simmons 2011[49] Ely cohort Fair	RCT 1 general practice United Kingdom	Phase 1 (1990-1999) A. Invited to screening with OGTT; rescreening at 5 and 10 years (n=1,705) A1. Attended screening (n=1,157/1,705; 68%) A2. Did not attend screening (n=548/1,705; 32%) B. No screening (n=3,231)	Phase 1 A vs B Mean age 53 vs 51 years 45% vs 51% male Race not reported Townsend Index of Deprivation Score -1.3 vs -1.5[c]	Phase 1 10 years	Phase 1 A vs B All-cause mortality: HR 0.96, 95% CI 0.77 to 1.20; aHR[d] 0.79 (95% CI 0.63 to 1.00) A1 vs B All-cause mortality: HR 0.64, 95% CI 0.47 to 0.86; aHR 0.54, 95% CI 0.40 to 0.74) A2 vs B All-cause mortality: HR 1.68, 95% CI 1.27 to 2.22; aHR 1.36, 95% CI 1.01 to 1.82
		Phase 2 (2000-2008)[e] A. Invited to screening A1. Attended screening (n=714/1,577; 45%) A2. Did not attend screening (n=863/1,577; 55%) B. No screening (n=1,425)	Phase 2 Population characteristics not reported; similar proportion of men and women in each group (data not reported)	Phase 2 8 years	Phase 2 A vs B All-cause mortality: HR 1.20, 95% CI 0.95 to 1.51; aHR 1.18, 95% CI 0.93 to 1.51 A1 vs B All-cause mortality: HR 0.46, 95% CI 0.311 to 0.69; aHR 0.52, 95% CI 0.35 to 0.78 A2 vs B All-cause mortality: HR 1.85, 95% CI 1.45 to 2.36; aHR 1.73, 95% CI 1.34 to 2.24

Table 6. Effect of Screening for DM on Health Outcomes

Author, Year Study Name Quality	Study Design Setting Country	Interventions	Population	Duration of Followup	Results
Rahman 2012[91] Ely cohort	RCT 1 general practice United Kingdom	A. Health assessment in people with diabetes previously screened (n=92) B. Health assessment in people with diabetes not previously screened (n=60)	A vs B Mean age: 68 vs 66 years 47% vs 46% female Race not reported Age at time of diabetes diagnosis 64 vs 64 years Time since diabetes diagnosis 5 vs 2 years (p=0.006) Proportion with screen-detected diabetes 93% vs 31%	12 years	A vs B Self-reported MI: 7/92 vs 8/60; RR 0.57, 95% CI 0.22 to 1.49 Self reported stroke: 3/92 vs 5/60; RR 0.39, 95% CI 0.10 to 1.58 Ischemic heart disease: 30/92 vs 28/60; RR 0.70, 95% CI 0.47 to 1.04 Nephropathy: 4/92 vs 1/60; RR 2.61, 95% CI 0.30 to 23) Peripheral neuropathy: 39/92 vs 32/60; RR 0.79, 95% CI 0.57 to 1.11 Peripheral vascular disease: 5/92 vs 2/60; RR 1.63, 95% CI 0.33 to 8.13 Mean SF-36[f] physical function score: 67.2 (SD 29.4) vs 69.6 (SD 30.7); p=0.64 Mean SF-36 mental health score: 77.8 (SD 16.5) vs 79.7 (SD 16.1); p=0.47

[a]Risk score determined using a previously validated model incorporating age, gender, BMI, use of steroids or antihypertensives, family history and smoking history.[68] A risk score of 0.35 was estimated to have 41% sensitivity, 86% specificity, 12% positive predictive value, and 96% negative predictive value.
[b]Higher score = higher level of deprivation.
[c]Score >0 = greater deprivation that the mean; <0 = less deprivation than the mean.
[d]Adjusted for age, sex and Index of Deprivation Score.
[e]Participants in Phase 2 were randomly selected from those not invited to screening in Phase 1.
[f]Short Form Health Survey, scale 0-100. Higher score = less disability.

Abbreviations: HR = adjusted hazard ratio; BMI = body mass index; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; OGTT = oral glucose tolerance test; RR = relative risk; SD = standard deviation.

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
Lifestyle interventions				
Andrews, 2011[95] 217 sites + community recruitment in the United Kingdom RCT Early ACTID Treatment duration and followup: 1 year	A. Intensive dietary advice and exercise (n=246) B. Intensive dietary advice (n=248) C. Usual care (n=99)	Patients with newly diagnosed DM **A vs B vs C** Mean age: 60 vs 60 vs 60 years Female sex: 36% vs 34% vs 37% Race: 94% vs 96% vs 97% White; other races not reported HbA1c: 6.7 vs 6.6 vs 6.7%	**A vs B vs C** All-cause mortality: 0% (0/246) vs 0% (0/248) vs 1%(1/99); A vs C: RR 0.14 (95% CI 0.01 to 3.31); B vs C: RR 0.14 (95% CI 0.01 to 3.29)	Good
Davies, 2008 [96] and Khunti 2012[97] 13 sites in the United Kingdom Cluster RCT DESMOND Treatment duration: one 6-hour education session one education session Followup: 3 years	A. Single, 6-hour group education session focusing on lifestyle, food, physical activity and cardiovascular risk factors + standard clinical management (n=437) B. Usual care (n=387)	Patients with newly diagnosed DM **A vs B** Mean age: 60 vs. 60 years Female sex: 47% vs. 43% (p<0.05) Race: 94% vs. 94% White; other races not reported HbA1c: 8.3% vs 7.9% (p<0.05)	**A vs B** Quality of life, WHOQOL-BREF – Overall satisfaction with quality of life: 4.0 vs. 4.0; p=0.48 Overall satisfaction with health: 4.0 vs. 4.0; p=0.94	Fair

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
Li, 2008[102] and Li 2014[110] 33 centers, China Cluster RCT Da Qing DPS Treatment duration: 6 years Followup: 23 years	A. Interventions - combined lifestyle, diet, or lifestyle + diet diet intervention: increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time physical activity (n=438) B. Control (n=138)	Patients with IGT **A vs. B** Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: NR Mean BMI: 25.7 vs. 26.2	**A vs. B: 20-year results** All-cause mortality: 25% (110/438) vs. 29% (40/138); HR 0.96; 95% CI 0.65 to 1.41 Cardiovascular mortality: 13% (57/438) vs 17% (23/138); HR 0.83, 95% CI 0.48 to 1.40 Cardiovascular events: 41% (180/438) vs 44% (61/138); HR 0.98; 95% CI 0.71 to 1.37 **A vs. B: 23-year results** All-cause mortality: 28% (121/430) vs. 38% (53/138); HR 0.71 (95% CI 0.51 to 0.99) Cardiovascular mortality: 12% (51/430) vs. 20% (27/138); HR 0.59 (95% CI 0.36 to 0.96)	Fair
Saito, 2011[107] 38 centers in Japan RCT Treament duration: 3 years Followup: 3 years	A. Individual lifestyle counseling session aimed at decreasing body weight and increasing physical activity with follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. Usual care (n=311)	Patients with IFG **A vs. B** Mean age: 50 vs 48 years Female sex: 28% vs 29% Race not reported Mean BMI 26.9 vs 27.1 kg/m2 Mean HbA1c 5.4% vs 5.4%	**A vs B** All-cause mortality: 0.3% (1/311) vs 0% (0/330); RR 3.18 (95% CI 0.13 to 78)	Fair
Uusitupa, 2009[107] Finnish DPS 5 centers in Finland RCT Followup: 11-14 years (varied by intervention group)	A. Intensive diet and counseling group (n=257) B. Control group (n=248)	Patients with IGT and BMI >25 kg/m^2 **A vs. B** Mean age: 55 vs. 55 Female sex: 66% vs. 68% Race not reported BMI: 31.4 vs. 31.2 kg/m^2	**A vs. B** All-cause mortality: 2.2 vs 3.8 events/1,000 person years; HR 0.57; 95% CI 0.21 to 1.58 Cardiovascular events: 22.9 vs 22.0 events/1,000 person-years; HR 1.04; 95% CI 0.72 to 1.51	Fair

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
Pharmacologic interventions				
DeFronzo, 2011[98] 8 centers in United States RCT Followup:: 2.4 years	A. Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Patients with IGT, BMI > 25, and ≥1 other RF diabetes **A vs. B** Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% vs 57% White; 26 vs 25% Hispanic; 19% vs 15% Black; 3% vs 3% other Mean BMI: 33.0 vs. 34.5 kg/m^2 Mean HbA1c: 5.5% vs. 5.5%	**A vs. B** All-cause mortality: 1% (3/303) vs. 0.3% (1/299); RR 2.96; 95% CI 0.31 to 28 Cardiovascular events: 9% (26/303) vs. 8% (23/299); RR 1.11; 95% CI 0.65 to 1.91	Fair
DREAM Trial Investigators, 2008[98] 191 centers in 21 countries RCT Followup:: 3 years	A. Ramapril 15 mg/day (n=2623) B. Placebo (n=2646) C. Rosiglitazone 0.8mg/day (n=2635) D. Placebo (n=2634) *Patients randomized twice, to ramapril or placebo and rosiglitazone or placebo*	Patients with IFG or IGT **A vs. B & C vs. D** Mean age: 55 vs. 55 years & 55 vs. 55 years Female sex: 60% vs. 59% & 58% vs. 60% Race not reported	**A vs. B** Total mortality: 1 % (31/2623) vs. 1% (32/2646); HR 0.98, 95% CI 0.60 to 1.61 Cardiovascular mortality: 0.5% (12/2623) vs. 0.4% (10/2646); HR 1.21, 95% CI 0.52 to 2.80 Cardiovascular events: 3% (69/2623) vs. 2% (64/2646); HR 1.09, 95% CI 0.78 to 1.53 MI: 0.5% (14/2623) vs. 0.4% (11/2646); HR 1.29, 95% CI 0.59 to 2.84 Stroke: 0.2% (4/2623) vs. 0.3% (8/2646); HR 0.50, 95% CI 0.15 to 1.66 Renal events: 14% (353/2623) vs 14% (365/2646); HR 0.97; 95% CI 0.83 to 1.14	Good

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
DREAM Trial Investigators, 2008[98] (continued)			**C vs D** Total mortality: 1% (30/2635) vs. 1% (33/2634); RR 0.91, 95% CI 0.56 to 1.49 Cardiovascular mortality: 0.5% (12/2635) vs. 0.4% (10/2634); HR 1.20, 95% CI 0.52 to 2.77 Cardiovascular events: 3% (77/2635) vs. 2% (56/2634); HR 1.38, 95% CI 0.98 to 1.95 MI: 0.6% (16/2635) vs. 0.3% (9/2634); HR 1.78, 95% CI 0.79 to 4.03 Stroke: 0.3% (7/2635) vs. 0.2% (5/2634); HR 1.40, 95% CI 0.44 to 4.40 Renal events: 7% (193/2635) vs 7% (185/2634); HR 1.18; 95% CI 0.88 to 1.57	
Kawamori, 2009[100] 103 centers in Japan RCT Treatment duration: 5 years Followup:: 3 years	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Patients with IFG **A vs. B** Mean age 56 vs. 56 years Female sex: 40% vs. 40% Race not reported	**A vs. B** All-cause mortality: 0.7% (6/897) vs. 0% (0/881); RR 13; 95% CI 0.72 to 226	Good

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
NAVIGATOR, 2010[102] (Nateglinide results) 806 centers in 40 countries RCT Followup:: 5 years	A. Nateglinide 60 mg/3 times daily (n=4645) B. Placebo (n=4661) *Patients also randomized in 2x2 factorial design to receive valsartan or placebo*	Patients with IGT and at least one CV risk factor or known CVD **A vs. B** Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% vs 83% White; 3% vs 3% Black; 7% vs 8% Asian; 8% vs 8% other Mean BMI: 30.5 vs. 30.5 kg/m^2 HbA1c: 5.8% vs. 5.8%	**A vs. B** All-cause mortality: 7% (310/4645) vs 7% (312/4661); RR 1.00; 95% CI 0.85 to 1.16; HR 1.00; 95% CI 0.85 to 1.17 Cardiovascular mortality: 3% (126/4645) vs. 4% (118/4661); RR 1.07; 95% CI 0.84 to 1.37; HR 1.07; 95% CI 0.83 to 1.38 Stroke: 4% (111/4645) vs 3% (126/4661); HR 0.89; 95% CI 0.69 to 1.15	Good
NAVIGATOR, 2010[103] (Valsartan results) 806 centers in 40 countries RCT Followup:: 5 years	A. Valsartan 160 mg/once daily (n=4631) B. Placebo (n=4675) *Patients also randomized in 2x2 factorial design to receive nateglinide or placebo*	Patients with IGT and at least one CV risk factor or known CVD **A vs. B** Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83% vs 83% White; 2% vs 3% Black, 6% vs 7% Asian, 8% vs 8% other Mean BMI: 30.4 vs. 30.6 kg/m^2 HbA1c: 5.8% vs. 5.8%	**A vs. B** All-cause mortality: 6% (295/4631) vs 12% (327/4675); HR 0.90; 95% CI 0.77 to 1.05 Cardiovascular mortality: 3% (128/4631) vs 3% (116/4675); HR 1.09; 95% CI 0.85 to 1.40 MI: 3% (138/4631) vs 3% (140/4675); HR 0.97; 95% CI 0.77 to 1.23 Heart failure requiring hospitalization: 2% (91/4631) vs 2% (94/4675); HR 0.97; 95% CI 0.72 to 1.29 Stroke: 2% (105/4631) vs 3% (132/4675); HR 0.79; 95% CI 0.61 to 1.02	Good

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
Nijpels, 2008[104] 1 center in The Netherlands RCT DAISI Treatment duration: 3 years	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	Patients with IGT **A vs. B** Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race not reported Mean BMI: 28.4 vs. 29.5 kg.m^2 HbA1c: 5.9% vs. 5.6%	**A vs. B** All-cause mortality: 2% (1/60) vs. 5 % (3/58); RR 0.32; 95% CI 0.03 to 3.01	Fair
Ramachandran, 2009[105] India RCT IDPP-2 Followup: 3 years	A. Pioglitazone (n=181) B. Placebo (n=186)	Patients with IGT **A vs. B** Mean age 45.1 vs. 45.5 Female sex: 13% vs. 14% Race not reported	**A vs. B** All-cause mortality: 1% (2/203) vs. 0.5% (1/203); RR 2.00; 95% CI 0.18 to 22 Cardiovascular mortality: 0.9% (2/204) vs 0% (0/203); RR 4.98; 95% CI 0.24 to 103	Fair
Zinman, 2010[108] 2 centers in Canada RCT CANOE Treatment duration: NR Followup: 4 years	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed dose combination (n=103) B. Placebo (n=104)	Patients with IGT and ≥one risk factor for DM **A vs. B** Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 75% vs 74% White; 8% vs 7% South Asian; 7% vs 7% Latino, 11% vs 13% other	**A vs. B** Myocardial infarction: 0% (0/103) vs. 1% (1/104), RR 0.34, 95% CI 0.01 to 8.17 Congestive heart failure: 0% (0/103) vs. 1% (1/104), RR 0.34, 95% CI 0.01 to 8.17	Good

Table 7. Health Outcomes in Studies of Interventions for Screen-Detected and Early Type 2 DM, IFG, or IGT

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Health Outcomes	Quality
Lifestyle and Pharmacologic Interventions				
Florez 2012[100] 27 centers in the U.S. RCT Diabetes Prevention Program Treatment duration: 3 years Followup: 5 years	A. Intensive lifestyle intervention, including diet and exercise to achieve modest weight reduction (n=1048) B. Metformin 850 mg/twice daily (n=1043) C. Placebo (n=1041)	Patients with IGT and BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans) **A vs B vs C** Mean age: 51 vs. 51 vs. 50 years Female sex: 68% vs. 66% vs. 69% Race: 54% vs 56% vs 54% White; 19% vs 21% vs 20% Black; 17% vs 15% vs 16% Hispanic; 9% vs 8% vs 10% Other	**A vs. C** Quality of life, SF-36 score changes from baseline, mean between-group difference: SF-6D: 0.0084 (SD 0.0041; p<0.05) PCS: 1.57 (SD 0.30; p<0.01) MCS: -0.29 (SD 0.32; p=NS) Physical function: 3.58 (SD 0.66; p<0.01) Body pain: 1.93 (SD 0.78; p<0.01) General health: 3.23 (SD 0.66; p<0.01) Vitality: 2.05 (SD 0.77; p<0.01) **B vs. C** Quality of life, SF-36 score changes from baseline, mean between-group difference: SF-6D: 0.0019 (SD 0.0041; p=NS) PCS: 0.15 (SD 0.30; p=NS) MCS: 0.22 (SD 0.32; p=NS) Physical function: 0.13 (SD 0.71; p=NS) Body pain: 0.50 (SD 0.78; p=NS) General health: 0.06 (SD 0.66; p=NS) Vitality: 0.09 (SD 0.76; p=NS)	Good

Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life Assessment, short version. Scale 1-5 for each domain; higher score = higher quality of life.

Table 8. Intensive Glucose Control and Health Outcomes in a Systematic Review of 14 Trials

Outcome	Number of Studies	Number of Patients		Relative Risk; 95% CI
		Intensive Control	Conventional Control	
All-Cause Mortality	12	1460/15142	1111/13217	1.02, 0.91 to 1.13; I^2=30%
Cardiovascular Mortality	12	765/15142	545/13217	1.11, 0.92 to 1.35; I^2=46%
Non-Fatal MI	8	644/15017	593/13094	**0.85, 0.76 to 0.95; I^2=0%**
Microvascular Outcomes[a]	3	1331/13770	1312/11830	**0.88, 0.79 to 0.97; I^2=45%**
Retinopathy	7	740/6175	660/4618	**0.80, 0.67 to 0.94; I^2=59%**
Nephropathy	8	3402/14675	3497/13094	0.83, 0.64 to 1.06; I^2=75%
Severe Hypoglycemia	9	1094/14887	380/12957	**2.39, 1.71 to 3.34; I^2=73%**

[a]Microvascular outcomes = presence or progression of nephropathy or retinopathy, end-stage renal disease, and retinal photocoagulation.

Abbreviations: CI = confidence interval; MI = myocardial infarction.

Table 9. Summary of Meta-Analyses of Intensive Versus Standard Blood Pressure Control in Persons With DM

	Number of Studies; Intensive vs. Standard Blood Pressure Control RR, 95% CI; I^2 (if reported)					
Study	**All-Cause Mortality**	**CV Mortality**	**Stroke**	**Myocardial Infarction**	**Heart Failure**	**Other Outcomes**
Bangalore, 2011[125]	**12 studies; 0.90, 0.82 to 0.98; I^2=0%** *Results stratified according to achieved SBP:* **SBP ≤135 mm Hg, 6 studies; 0.87, 0.79 to 0.95; I^2=0%** SBP ≤130 mm Hg, 6 studies; 1.04, 0.86 to 1.25; I^2=0%	7 studies; 0.93, 0.82 to 1.06; I^2=7% *Results stratified according to achieved SBP:* SBP ≤135 mm Hg, 4 studies; 0.90, 0.78 to 1.03; I^2=29% SBP ≤130 mm Hg, 3 studies; 1.11, 0.82 to 1.52; I^2=0%	**9 studies; 0.83, 0.73 to 0.95; I^2=27%** *Results stratified according to achieved SBP:* SBP ≤135 mm Hg, 5 studies; 0.90, 0.78 to 1.03; I^2=0% **SBP ≤130 mm Hg, 4 studies; 0.53, 0.38 to 0.75; I^2=0%**	8 studies; 0.92, 0.80 to 1.06; I^2=0% *Results stratified according to achieved SBP:* SBP ≤135 mm Hg, 4 studies; 0.92, 0.76 to 1.11; I^2=13% SBP ≤130 mm Hg, 4 studies; 0.92, 0.80 to 1.06; I^2=0%	6 studies; 0.90, 0.75 to 1.06; I^2=48% *Results stratified according to achieved SBP:* SBP ≤135 mm Hg, 3 studies; 0.82, 0.66 to 1.02; I^2=45% SBP ≤130 mm Hg, 3 studies; 1.03, 0.78 to 1.35; I^2=54%	**Nephropathy: 5 studies; 0.73, 0.64 to 0.84; I^2=61%** *Results stratified according to achieved SBP:* SBP ≤135 mm Hg, 3 studies; 0.83, 0.68 to 1.00; I^2=0% **SBP ≤130 mm Hg, 2 studies; 0.64, 0.53 to 0.78; I^2=83%**
Reboldi, 2011[134]			**5 studies; 0.61, 0.48 to 0.79; I^2=0%**	5 studies; 0.87, 0.74 to 1.02; I^2=0%		

Abbreviations: CI = confidence interval; CV = cardiovascular; RR = relative risk; SBP = systolic blood pressure.

Table 10. Trials of Variably Defined Intensive Versus Standard Blood Pressure Control in Persons With DM

			Intensive vs. Standard BP Lowering, RR (95% CI)				
Study n Duration of Followup	**Interventions**	**BP: Baseline; Target; Achieved (mm Hg)**	**All-Cause Mortality**	**CV Mortality**	**Stroke**	**Myocardial Infarction**	**Other Outcomes**
ABCD (H)[74]* n=470 5 years	Intensive: nisoldipine or enalapril, plus open label antihypertensives to achieve target DBP Standard: nisoldipine or enalapril	Baseline Intensive: 156/98 Standard: 154/98 Target Intensive: DBP ≤75 Standard: DBP 80-89 Achieved Intensive: 132/78 Standard: 138/86	6% (13/237) vs 10% (25/233); 0.51 (0.27 to 0.97)			7% (16/237) vs 6% (14/233); 1.12 (0.56 to 2.25)	Nephropathy: 7% (16/237) vs 10% (23/233); 0.68 (0.37 to 1.26)
ABCD (N)[75]* n=480 5 years	Intensive: nisoldipine 10-60mg/day or enalapril 5-40 mg/day Standard: placebo	Baseline Intensive: 136/84 Standard: 137/84 Target Intensive: DBP decrease of ≥10 Standard: no DBP decrease (DBP 80-89) Achieved Intensive: 128/75 Standard: 137/81	8% (18/237) vs 8% (20/243); 0.92 (0.50 to 1.70)	5% (13/237) vs 4% (9/243); 1.48 (0.65 to 3.40)	2% (4/237) vs 5% (13/243); 0.32 (0.10 to 0.95)	8% (19/237) vs 6% (15/243); 1.30 (0.68 to 2.50)	Congestive heart failure: 5% (12/237) vs 5% (11/243); 1.12 (0.50 to 2.49)
ACCORD[79] n=4732 5 years	Intensive: use of antihypertensives necessary to reach target according to a prespecified treatment algorithm Standard: usual care	Baseline Intensive:139/76 Standard: 139/76 Target Intensive: SBP <120 Standard: SBP <140 Achieved Intensive: 119/64 Standard: 134/71	6% (150/2363) vs 6% (144/2371); 1.11 (0.89 to 1.38)	3% (60/2363) vs 2% (58/2372); 1.04 (0.73 to 1.48)	2% (36/2363) vs 3% (62/2371); 0.58 (0.39 to 0.88)	5% (126/2362) vs 6% (146/2371); 0.87 (0.69 to 1.09)	Fatal or nonfatal heart failure: 4% (83/2363) vs 4% (90/2371); 0.93 (0.69 to 1.24) Loss of visual acuity: 35% (819/2339) vs 36% (849/2352); 0.97 (0.90 to 1.05) Score >2 on Michigan Neuropathy Screening Instrument: 53% (722/1353) vs 56% (781/1388); 0.95 (0.89 to 1.02)

Table 10. Trials of Variably Defined Intensive Versus Standard Blood Pressure Control in Persons With DM

			Intensive vs. Standard BP Lowering, RR (95% CI)				
Study n Duration of Followup	**Interventions**	**BP: Baseline; Target; Achieved (mm Hg)**	**All-Cause Mortality**	**CV Mortality**	**Stroke**	**Myocardial Infarction**	**Other Outcomes**
ADVANCE[80] n=11140 4 years	Intensive: addition to existing BP regimen of fixed-dose combination of perindopril-indapamide; no target set Standard: existing BP regimen with addition of placebo	Baseline Intensive: 145/81 Standard: 145/81 Target Intensive: No target Standard: No target Achieved Intensive: 136/73 Standard: 140/73	7% (408/5569) vs 9% (471/5571); 0.87 (0.76 to 0.98)	4% (211/5569) vs 5% (257/5571); 0.82 (0.69 to 0.98)			Renal events: 22% (1243/5569) vs 27% (1500/5571); 0.83 (0.78 to 0.89) New or worsening retinopathy: 5% (289/5569) vs 5% (286/5571); 1.01 (0.86 to 1.19) New or worsening nephropathy: 3% (181/5569) vs 4% (216/5571); 0.84 (0.69 to 1.02)
HOT[73]* n=1501 with DM 4 years	Intensive: felodipine + others added incrementally if needed to reach target Standard: felodipine	Baseline Intensive: 170/105 Standard: 170/105 Target Intensive: DBP ≤80 Standard: DBP ≤85 or 90 Achieved Intensive: 140/81 Standard: 143/84	3% (17/499) vs 6% (59/1002); 0.58 (0.34 to 0.94)	1% (7/499) vs 4% (42/1002); 0.33 (0.15 to 0.74)	2% (12/499) vs 3% (30/1002); 0.80 (0.41 to 1.56)	3% (15/499) vs 3% (34/1002); 0.89 (0.49 to 1.61)	
UKPDS[72]* n=1148 8 years	Intensive: captopril or atenolol + others added incrementally if needed to reach target Standard: no use of ACE inhibitors or beta blockers	Baseline Intensive: 160/93 Standard: 160/93 Target Intensive: <150/85 Standard: <180/105 Achieved Intensive: 143/79 Standard: 152/22	18% (134/758) vs 21% (83/390); 0.83 (0.65 to 1.06)		5 %(38/758) vs 9% (34/390); 0.58 (0.37 to 0.90)	14% (107/758) vs 18% (69/390); 0.80 (0.60 to 1.05)	Diabetes-related death: 11% (82/758) vs 16% (62/390); 0.68 (0.50 to 0.92)
UKPDS n=1148 16 years (8 years on trial + 8 years post-trial monitoring)			49% (373/758) vs 54% (211/390); 0.89 (0.75 to 1.06)		12% (90/758) vs 15% (58/390); 0.77 (0.55 to 1.07)	27% (205/758) vs 29% (115/390); 0.90 (0.71 to 1.13)	Diabetes-related death: 27% (203/758) vs 31% (122/390); 0.84 (0.67 to 1.05)

*Included in previous USPSTF reviews.

Abbreviations: BP = blood pressure; CI = confidence interval; CV = cardiovascular; RR = relative risk; SBP = systolic blood pressure.

Table 11. Effects of Multifactorial Interventions on Health Outcomes in Persons with DM Not Specifically Screen-Detected

Study Followup n	Target Values		Baseline Values		Values at End of Followup		Outcomes Intensive vs. Standard Control[a]
	Intensive Group	Standard Group	Intensive Group	Standard Group	Intensive Group	Standard Group	
ADVANCE[130] 4 years n=5566	HbA1c: ≤6.5% BP: no target	Usual care targets	HbA1c: 7.5% BP: 145/81 mm Hg	HbA1c: 7.5% BP: 145/81 mm Hg	HbA1c: 6.9% BP: 138/78 mm Hg	HbA1c: 7.5% BP: 145/81 mm Hg	All-cause mortality: 7% (198/2783) vs 9% (240/2783); **RR 0.83 (95% CI 0.70 to 0.99)** CV mortality: 4% (104/2783) vs 5% (136/2783); **RR 0.76 (95% CI 0.60 to 0.98)**
JEDIT[148] 6 years n=1173	HbA1c: <6.9% BP: <130/85 mm Hg TC: <180 mg/dL	Usual care targets	HbA1c: 8.4% BP: 138/74 TC: 202 mg/dL	HbA1c: 8.5% BP: 137/75 mm Hg TC: 202 mg/dL	HbA1c: 7.7% BP: 134/71[b] mm Hg TC: 188 mg/dL	HbA1c: 7.8% BP: 134/71 mm Hg TC: 190 mg/dL	*Events and p-values of between-group comparisons (numbers for groups NR)* Death due to diabetes: 35 events (p=0.85) Death not related to diabetes: 59 events (p=0.30) Fatal MI: 12 events (p=0.08) Sudden death: 13 events (p=0.99) Fatal stroke: 6 events (p=0.66) Death due to renal failure: 3 events (p=0.08) Death due to hyper/hypoglycemia: 1 event (p=0.32) Nonfatal MI: 17 events (p=1.0) Any stroke: 67 events (p=0.29)
SANDS[152, 153] 3 years n=499	BP: ≤115/75 mm Hg LDL-C: <70 mg/dL Non-HDL-C: <100 mg/dL	BP: <130/85 mm Hg LDL-C: <100 mg/dL Non-HDL-C: <130 mg/dL	BP: 128/74 mm Hg LDL-C: 104 mg/dL Non-HDL-C: 138 mg/dL	BP: 133/76 mm Hg LDL-C: 104 mg/dL Non-HDL-C: 140mg/dL	BP: 117/67[b] mm Hg LDL-C: 72 mg/dL Non-HDL-C: 102 mg/dL	BP: 129/73[b] mm Hg LDL-C: 104 mg/dL Non-HDL-C: 138 mg/dL	Non-CV death: 0.8% (2/252) vs. 2% (4/247); RR 0.49 (95% CI 0.09 to 2.65)
Steno-2[131] 13 years n=160	HbA1c: <6.5% BP: <130/80 mm Hg TC: <150 mg/dL	Usual care targets	HbA1c: 8.4% BP: 146/85 mm Hg TC: 210 mg/dL	HbA1c: 8.8% BP: 149/86 mm Hg TC: 233 mg/dL	HbA1c: 7.7% BP: 140/74[b] mm Hg TC: 147[b] mg/dL	HbA1c: 8.0% BP: 146/73[b] mm Hg TC: 155 mg/dL	All-cause mortality: 30% (24/80) vs. 50% (40/80); **RR 0.60 (95% CI 0.40 to 0.90)** CV mortality: 11% (9/80) vs. 24% (19/80); **RR 0.47 (95% CI 0.23 to 0.98)** MI: 10% (8/80) vs. 26% (21/80); **RR 0.38 (95% CI 0.18 to 0.81)** Stroke: 8% (6/80) vs. 23% (18/80); **RR 0.33 (95% CI 0.14 to 0.80)** Nephropathy: 25% (20/80) vs. 46% (37/80); **RR 0.44 (95% CI 0.25 to 0.77)** Retinopathy: 51% (41/80) vs. 68% (54/80); **RR 0.57 (95% CI 0.37 to 0.88)**

[a]Additional outcomes reported in Appendix B10.
[b]Target achieved; in some cases values were lower than target levels at baseline.

Abbreviations: BP = blood pressure; CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction NR = not reported; RR = relative risk; TC = total cholesterol.

Table 12. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Progression to Diabetes	Quality
Lifestyle interventions				
Katula, 2013[172] Community setting, United States RCT Treatment duration: 2 years	A. Intensive lifestyle intervention (n=151) B. Usual care (n=150)	Overweight or obese patients with IFG **A vs. B** Mean age: 57.3 vs. 58.5 years Female sex: 58% vs. 57% Race: 73.5% White, 25.8% Black, 0.7% other vs. 74% White, 23.3% Black, 2.7% other Mean BMI: 32.8 vs. 32.6	**A vs. B** Incidence: 2.6% (4/151) vs. 7.3% (11/150); RR 0.36, 95% CI 0.12 to 1.11	Fair
Li, 2008[102] and Li 2014[110] 33 centers, China Cluster RCT Da Qing DPS Treatment duration: 6 years Followup: 20 years (mean 9.4 years)	A. Interventions - combined lifestyle, diet, or lifestyle + diet diet intervention: increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time physical activity (n=438) B. Control (n=138)	Patients with IGT **A vs. B** Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: NR Mean BMI: 25.7 vs. 26.2	**A vs. B: 20-year results** Incidence: 6.9 vs. 11.3 cases/100 person-years per year Cumulative incidence: 79.7% (349/438) vs. 92.8% (128/138); RR 0.86, 95% CI 0.80 to 0.92 Adjusted hazard rate ratio: 0.57, 95% CI 0.41 to 0.81 NNT: 6 **A vs. B: 23-year results** Incidence: 7.3 vs. 12.3 cases/100 person-years per year Cumulative incidence: 73% (312/430) vs. 90% (124/138); RR 0.86, 95% CI 0.80 to 0.92 Adjusted hazard rate ratio: 0.55, 95% CI 0.40 to 0.76	Fair
Lindahl, 2009[171] Single center, Sweden Vasterbotten Intervention Programme Treatment duration: 1 year Followup: 5 years	A. Intensive lifestyle intervention, including a month-long stay in a wellness center and four-day followup one year later (n=83) B. Usual care (n=85)	Patients with IGT and BMI >27 **A vs. B** Mean age: 52 vs. 54 years Female sex: 70% vs. 61% Race: NR Mean BMI: 31.2 vs. 30.2	**A vs. B** Incidence at one year (end of intervention): 6% (5/83) vs. 23.5% (20/85); RR 0.26, 95% CI 0.10 to 0.65 Incidence at three years: 14.5% (12/83) vs. 23.5% (20/85); RR 0.61, 95% CI 0.32 to 1.18 Incidence at five years: 20% (17/83) vs. 27% (23/85); RR 0.75, 95% CI 0.44 to 1.31	Fair

Table 12. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Progression to Diabetes	Quality
Penn, 2009[169] United Kingdom RCT EDIPS Treatment duration: Up to 5 years Median followup: 3.1 years	A. Biweekly sessions for 1 month and monthly for 3 months, and every 3m for up to 5 years; Motivational interview from dietician and physiotherapist with quarterly newsletter and advice to target >50% energy from carbohydrates (n=51) B. One session of health promotion advice (n=51)	Patients with IGT and BMI>25 **A vs. B** Mean age: 56.8 vs. 57.4 years Female sex: 59% vs. 61% Race: NR	**A vs. B** Incidence: 9.8% (5/51) vs. 21.6% (11/51); RR 0.45, 95% CI 0.17 to 1.21 Incidence rate per 1,000 persons: 32.7 vs. 67.1	Fair
Saito, 2011[107] 38 centers in Japan RCT Zensharen Study for Prevention of Lifestyle Diseases Treatment duration: 5 years and 3 months Mean followup: 2.7 years	A. Individual session and goal to decrease weight by 5% with follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. One session advise to reduce weight by 5% (n=311)	Patients with IGT and BMI > 24 **A vs. B** Mean age: 50 vs. 48 Female sex: 28% vs. 29% Race: NR	**A vs. B** Cumulative incidence: 10.6% (35/330) vs. 16.4% (51/311); RR 0.65, 95% CI 0.43 to 0.97	Fair
Sakane, 2011[170] 32 community clinics in Japan RCT JDPP Treatment duration: 6 years Followup: 3 years	A. Individual and group sessions (4 group session lasting 2-3 hrs, biannual individual session lasting 20-40 min) (n=146) B. One group session (n=150)	Patients with IGT **A vs. B** Mean age: 51 years Female sex: 50% vs. 49% Race: NR	**A vs. B** Incidence: 6.1% (9/146) vs. 12% (18/150); RR 0.51, 95% CI 0.24 to 1.11	Fair

Table 12. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Progression to Diabetes	Quality
Pharmacologic interventions				
Armato, 2012[165] United States Prospective Cohort Mean followup: 6.9 vs. 5.5 vs. 8.9 months	A. Pioglitazone 15 mg/day and metformin 850 mg/day (n=40) B. Pioglitazone 15 mg/day, metformin 850 mg/day, and exenatide 10 mcg/twice daily (n=47) C. Lifestyle counseling, including weight loss 7% over 3 months, diet information, walking 30 minutes per day 7 days per week (n=18)	Patients with IFG or IGT **A vs. B** Mean age: 62 vs. 56 vs. 61 years; p=0.03 Female sex: 28% vs. 43% vs. 39% Race: 82.5% White, 2.5% Black, 15% other vs. 83% White, 2.1% Black, 14.9% other vs. 100% White Mean BMI: 27.0 vs. 29.7 vs. 27.5 HbA1c: 5.8 vs. 5.7 vs. 5.6	**A vs. B vs. C** Incidence: 0 vs. 0 vs. 5.6% (1/18); A vs. C, RR 0.15, 95% CI 0.01 to 3.62; B vs. C, RR 0.13, 95% CI 0.01 to 3.10	Fair
DeFronzo, 2011[98] 8 centers in United States RCT Median followup: 2.4 years	A. Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Patients with IGT, BMI > 25, and ≥1 other RF diabetes **A vs. B** Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% White, 26% Hispanic, 19% Black, 3% other vs. 57% White, 25% Hispanic, 15% Black, 3% other Mean BMI: 33.0 vs. 34.5 Mean HbA1c: 5.5 vs. 5.5	**A vs. B** Incidence: 5.0% (15/303) vs. 16.7% (50/299); RR 0.30, 95% CI 0.17 to 0.52 Annual average incidence: 2.1% vs. 7.6%; p<0.001 HR: 0.28 (95% CI 0.16 to 0.49) NNT for duration of trial (2.2 years): 8 NNT for one year: 18	Fair
Kawamori, 2009[101] 103 centers in Japan RCT Treatment duration: 5 years Mean followup: 3 years	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Patients with IFG **A vs. B** Mean age 55.7 vs. 55.7 years Female sex: 40% vs. 40% Race: NR	**A vs. B** Incidence 5.5% (50/897) vs. 12% (106/881); RR 0.46, 95% CI 0.34 to 0.64 HR: 0.595	Good
Lindblad, 2011[168] 23 centers in Sweden RCT Median followup: 3.7 years	A. Glimepiride 1 mg/day (n=136) B. Placebo (n=138)	Patients with IFG **A vs. B** Mean age: 60.4 vs. 59.6 years Female sex: 35.3% vs. 45.7% Race: NR Mean BMI: 29.9 vs. 29.6 Mean HbA1c: 4.9 vs. 4.9	**A vs. B** Incidence: 30.1% (41/136) vs. 39.9% (55/138); RR 0.76, 95% CI 0.55 to 1.05 Incidence, adjusted for baseline HbA1c, proinsulin, and CRP: OR 0.62 (p=0.028)	Fair

Table 12. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Progression to Diabetes	Quality
NAVIGATOR, 2010[103] (Nateglinide results) 806 centers in 40 countries RCT Median followup: 5 years	A. Nateglinide 60 mg/3 times daily (n=4645) B. Placebo (n=4661) *Patients also randomized in 2x2 factorial design to receive valsartan or placebo	Patients with IGT and at least one CV risk factor or known CVD **A vs. B** Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% White, 2.6% Black, 6.7% Asian, 7.8% other vs. 83.2% White, 2.5% Black, 6.5% Asian, 7.8% other Mean BMI: 30.5 vs. 30.5	**A vs. B** Incidence: 36.0% (1647/4645) vs. 33.9% (1580/4661); RR 1.05, 95% CI 0.99 to 1.11 Absolute hazard difference: 6.18 (95% CI 0.47 to 11.90) HR: 1.07 (95% CI 1.00 to 1.15)	Good
NAVIGATOR, 2010[104] (Valsartan results) 806 centers in 40 countries RCT Median followup: 5 years	A. Valsartan 160 mg/once daily (n=4631) B. Placebo (n=4675) *Patients also randomized in 2x2 factorial design to receive nateglinide or placebo	Patients with IGT and at least one CV risk factor or known CVD **A vs. B** Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83.1% White, 2.4% Black, 6.4% Asian, 8.0% other vs. 83.1% White, 2.6% Black, 6.7% Asian, 7.5% other Mean BMI: 30.4 vs. 30.6 HbA1c: 5.8 vs. 5.8	**A vs. B** Incidence: 33.1% (1532/4631) vs. 36.8% (1722/4675); RR 0.90, 95% CI 0.85 to 0.95 Absolute hazard difference: -12.6 (95% CI -18.4 to -6.9) HR: 0.86 (95% CI 0.80 to 0.92)	Good
Nijpels, 2008[105] 1 center in The Netherlands RCT DAISI Treatment duration: 3 years	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	Patients with IGT **A vs. B** Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race: NR Mean BMI: 28.4 vs. 29.5 HbA1c: 5.9 vs. 5.6	**A vs. B** Incidence: 18.3% (11/60) vs. 24.1% (14/58); RR 0.76, 95% CI 0.38 to 1.53 Attributable risk: -0.14 (95% CI -0.46 to 0.21) Absolute risk reduction: 6% (95% CI -9% to 21%)	Fair
Ramachandran, 2009[106] India RCT IDPP-2 Mean followup: 3 years	A. Pioglitazone (n=181) B. Placebo (n=186)	Patients with IGT **A vs. B** Mean age 45.1 vs. 45.5 Female sex: 13% vs. 14% Race: NR	**A vs. B** Cumulative incidence: 29.8% (54/181) vs. 31.6% (59/186); RR 0.94, 95% CI 0.69 to 1.28	Fair

Table 12. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Country Study Design Study Name Treatment Duration Followup	Intervention and Comparison	Population	Progression to Diabetes	Quality
Zinman, 2010[109] 2 centers in Canada RCT CANOE Treatment duration: NR Median followup: 3.9 years	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed dose combination (n=103) B. Placebo (n=104)	Patients with IGT and >one risk factor for DM **A vs. B** Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 74.8% White, 7.8% South Asian, 6.8% Latino, 10.7% other vs. 74% White, 6.8% South Asian, 6.7% Latino, 12.5% other	**A vs. B** Incidence: 13.6% (14/103) vs. 39.4% (41/104); RR 0.34, 95% CI 0.20 to 0.59 RR reduction: 66% (95% CI 41-80%) Absolute risk reduction: 26% (95% CI 14-37%) NNT over 3.9 years: 4 (95% CI 2.7-7.1) Hazard ratio: 0.31 (95% CI 0.17 to 0.58)	Good
Multifactorial interventions				
Lu, 2011[166] 4 communities in China RCT Treatment duration: 2 years	A. IGT - acarbose 50 mg/3 times daily; IFG or IGT/IFG - metformin 250 mg/3 times daily; anti-hypertensives, antidyslipidemia agents, and aspirin (n=95) B. Control – health/diabetic education once a month (n=86)	Patients with IGT and BMI>19 **A vs. B** Mean age: 62 vs. 65 years Female sex: 47% vs. 48% Race: NR Mean BMI: 27.1 vs. 26.9 HbA1c: 5.9 vs. 6.0	**A vs. B** Incidence: 0% vs. 5.8% (5/86); RR 0.08, 95% CI 0.00 to 1.42	Fair
Rasmussen, 2008[167] Multicenter, Denmark Cluster RCT ADDITION	A. Intensive management, including lifestyle advice, aspirin, drug treatment of blood glucose, blood pressure, and lipids according to strict targets (n=865) Subgroup got motivational interviewing training B. Standard care (n=645)	Patients with IGT or IFG, high risk based on a self-administered questionnaire **A vs. B** <u>IFG</u> Mean age: 60 vs. 60 years Female sex: 43% vs. 43% Race: NR Mean BMI: 29.1 vs. 29.1 <u>IGT</u> Mean age: 61 vs. 61 years Female sex: 53% vs. 60% Race: NR Mean BMI: 29.5 vs. 29.8	**A vs. B** Incidence: 14.1 vs. 15.8 cases/100 person-years; RR 0.89, 95% CI 0.78 to 1.02 <u>Sub-analyses</u> Motivational interviewing + intensive intervention: RR 0.83, 95% CI 0.68-1.00 Intensive treatment alone: RR 0.95, 95% CI 0.80 to 1.14 IFG: RR 0.90, 95% CI 0.73 to 1.12 IGT: RR 0.90, 95% CI 0.77 to 1.07	Fair

Abbreviations: ADDITION = Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; BMI = body mass index; CANOE = Canadian Normoglycemia Outcomes Evaluation; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DAISI = Dutch Acarbose Intervention Study in Persons With Impaired Glucose Tolerance; DM = diabetes mellitus; DPS = Diabetes Prevention Study; EDIPS = European Diabetes Prevention Study; HR = hazard ratio; IDPP-2 = Indian Diabetes Prevention Program-2; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; JDPP = Japanese Diabetes Prevention Program; NNT = number needed to treat; RCT = randomized, controlled trial; RR = relative risk.

Table 13. Summary of Evidence

Main Findings from Previous USPSTF Report	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 1. Is there direct evidence that screening for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance among asymptomatic, nonpregnant adults improves health outcomes?						
No RCTs on the effects of screening for DM on clinical outcomes. One case-control study found no association between screening and improvement in microvascular outcomes	2 RCTs	Mortality outcomes limited to 10 years	Consistent	Both trials in UK; ADDITION in high risk population; Ely trial in average risk population	Two RCTs found no effect on all-cause or cardiovascular mortality with screening versus no screening after 10 years.	Fair
Key Question 2. What are the harms of screening nonpregnant adults for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?						
No evidence on serious psychological or other adverse effects associated with a new diagnosis of DM	3 RCTs	Small sample size in study demonstrating short-term anxiety associated with invitation to screening	Consistent	All trials in UK; 2 studies in high risk population; 1 in average risk population	In the short-term (6-14 weeks), being invited to screening increased anxiety versus not being invited; at 13 years no difference in anxiety or depression between those screening negative for diabetes and those unscreened; at 12 months there was no difference in anxiety or depression in those screened positive for diabetes versus those who screened negative	Fair
Key Question 3. Do interventions for screen-detected or mild type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance provide an incremental benefit in health outcomes compared with no interventions or initiating interventions after clinical diagnosis?						
No clear evidence on benefit of treatment in screen-detected DM population or comparing treatment effects in people with screen- and clinically-detected DM although one trial found acarbose associated with reduced risk of MI	13 RCTs (16 publications)	Some studies underpowered to evaluate mortality and other CV outcomes; most studies limited to three year followup; evidence often limited to a single study per drug	Consistent	Few studies in a non-white population Some studies required patients to have CV disease or risk factor for DM or CV disease; other studies excluded patients with CV disease	Most studies found no benefit on all-cause or cardiovascular mortality with glucose-lowering or antihypertensive medications or with lifestyle modification, though one study of lifestyle modification found reduced risk of all-cause and cardiovascular mortality after 23 years followup. Lifestyle modification improved general health scores	Fair

Table 13. Summary of Evidence

Main Findings from Previous USPSTF Report	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 4. What are the harms of interventions for screen-detected or mild type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?						
No studies reported serious harms No studies conducted in people with screen-detected DM reporting harms. Studies conducted in people with IFG or IGT included in the prior report found no differences in withdrawal rates between lifestyle or pharmacologic interventions and control.	9 RCTs (11 publications)	Few studies in screened-detected or early DM, IFG or IGT populations	Consistent	Few studies in a non-white population Some studies required patients to have CV disease or risk factor for DM or CV disease; other studies excluded patients with CV disease	Little difference between active medication or lifestyle modification versus placebo or usual care in risk of harms. Acarbose was associated with greater withdrawal rates; Single study evidence for: increased risk of any adverse event with pioglitazone and voglibose, increased hypoglycemia with nateglidine and increased hypotension with valsartan; No trial of metformin reported risk of lactic acidosis	Fair
Key Question 5. Is there evidence that more intensive glucose, blood pressure or lipid control interventions improve health outcomes in nonpregnant adults with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance compared to traditional control? Is there evidence that aspirin use improves health outcomes in these populations compared to nonuse?						
No evidence in a screen-detected DM population. Studies that enrolled people with established DM found no clear evidence of a differential effect on individual health outcomes with intensive blood pressur or lipid lowering, or with aspirin for primary preventio of CVD.	<u>People with screen-detected DM</u> 3 RCTs (4 publications) <u>People with DM not specifically screen-detected</u> 13 systematic reviews 10 RCTs (33 publications)	Some studies were underpowered as event rates were lower than anticipated Limited evidence in people with IFG, IGT and screen-detected DM	<u>People with screen-detected DM</u> Consistent <u>People with DM not specifically screen-detected</u> Glucose control: consistent Blood pressure control: inconsistent Lipid lowering: N/A	Only 1 fair-quality trial enrolled people with screen-detected diabetes; other studies enrolled people with established DM	<u>People with screen-detected DM</u> Use of an intensive multifactorial glucose, blood pressure and lipid lowering intervention did not significantly reduce risk of all-cause or CV mortality, MI, stroke or revascularization after 5 years followup. <u>People with DM not specifically screen-detected</u> Intensive glucose-lowering did not significantly decrease risk of all-cause or CV mortality, but was associated with a significant reduction in risk of nonfatal MI in systematic reviews. Intensive BP lowering reduced risk of all-cause mortality and stoke in a good-quality systematic review, but results from recently published trials were mixed on the effect on health outcomes, though different interventions and blood pressure targets were	Good

Table 13. Summary of Evidence

Main Findings from Previous USPSTF Report	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
			Multifactorial intervention: inconsistent Aspirin: consistent		used in these studies. Intensive lipid lowering did not significantly reduce risk of most health outcomes though evidence was very limited. Evidence for use of an intensive multifactorial intervention was mixed; 2 trials found a significant benefit on health outcomes while 2 others did not. Aspirin did not reduce incidence of health outcomes based on 2 good-quality systematic reviews.	
Key Question 6. What are the harms of more intensive interventions compared to traditional control in people with screen-detected or early type 2 diabetes, impaired fasting glucose or impaired glucose tolerance?						
Not assessed	5 systematic reviews 6 RCTs	Trials generally not designed to assess harms; interventions and targets varied	Consistent for effects of glucose-lowering therapy; inconsistent for blood pressure lowering therapy	Unclear; no evidence in screen-detected population	Intensive glucose lowering was consistently associated with increased risk of severe hypoglycemia. Evidence on harms of intensive blood pressure lowering was mixed. Aspirin use increased risk of bleeding in a systematic review of 6 trials.	Fair
Key Question 7. Do interventions for impaired fasting glucose or impaired glucose tolerance delay or prevent the progression to type 2 diabetes?						
6 studies of lifestyle interventions and 8 studies of pharmacologic interventions found some evidence that intervention delays or prevents progression	Multifactorial interventions: 2 RCTs Lifestyle interventions: 6 RCTs (in 7 publications) Pharmacologic interventions: 8 RCTs (in 9 publications)	Some studies underpowered, lack of blinding in many studies, content of interventions varied widely	Multifactorial interventions: Consistent Lifestyle interventions: Consistent Pharmacologic interventions: Consistent	Few studies reported race/ethnicity, but effects were largely consistent among studies in various countries	Two studies of multifactorial interventions found no effect on risk of progression to diabetes, though the estimate of one study was imprecise Three of six studies of lifestyle interventions found reduced risks of progression to diabetes among intervention participants, and three other studies had point estimates in favor of the interventions that failed to reach significance Four studies of pharmacologic interventions found reduced risk of progression to diabetes among intervention groups receiving	Good

Table 13. Summary of Evidence

Main Findings from Previous USPSTF Report	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
					thiazolinediones, alpha-glucosidase inhibitors, metformin, and valsartan. Nateglinide was evaluated in one study that reported no effect, glimepiride was not found to be effective at delaying progression, and exenatide was reported in one small study with imprecise estimates.	
Key Question 8. Do the effects of screening or interventions for screen-detected or mild type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance vary by subgroups, such as age, sex, or race/ethnicity?						
No evidence on how the effects of screening or treatment of screen-detected DM, IFG or IGT varies according to subgroup	1 systematic review, 4 RCTs	No study designed to assess subgroup differences. Available evidence too limited to draw conclusions		No evidence in screen-detected population	No direct evidence on the effect of screening in subgroups though men (but not women) who underwent screening and died during followup had significantly longer life compared to those who were not screened. Based on 1 study, intensive glucose lowering increased risk of mortality in people <age 65 years (but not in older people) and in Blacks (but not Whites, Hispanics or Asians). Intensive lipid lowering reduced risk of CV events in men but not women, and aspirin use reduced risk of MI in men.	Poor

[a]"Overall quality" is based on new evidence identified for this update plus previously reviewed evidence.

Abbreviations: ADDITION = Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; MI = myocardial infarction; RCT = randomized, controlled trial; UK = United Kingdom.

KQ 1-2

Ovid MEDLINE(R) without Revisions 1996 to January Week 1 2013
1. exp Diabetes Mellitus, Type 2/
2. Prediabetic State/
3. Glucose Intolerance/
4. ("impaired fasting glucose" or "ifg").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. ("impaired glucose tolerance" or "itg").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. prediabet$.mp.
7. or/1-6
8. Mass Screening/
9. screen$.ti.
10. 8 or 9
11. 7 and 10
12. Pregnancy/
13. 11 not 12
14. limit 13 to yr="2007 - 2013"
15. limit 14 to "all adult (19 plus years)"
16. limit 15 to english language
17. limit 15 to abstracts
18. 16 or 17

Cochrane Central Register of Controlled Trials January 2013
1. exp Diabetes Mellitus, Type 2/
2. Prediabetic State/
3. Glucose Intolerance/
4. ("impaired fasting glucose" or "ifg").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. ("impaired glucose tolerance" or "itg").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. prediabet$.mp.
7. or/1-6
8. Mass Screening/
9. screen$.ti.
10. 8 or 9
11. 7 and 10
12. Pregnancy/
13. 11 not 12
14. limit 13 to yr="2007 – 2013

KQ 3-6

Ovid MEDLINE(R) without Revisions 1996 to January Week 1 2013
1. exp Diabetes Mellitus, Type 2/
2. Prediabetic State/
3. Glucose Intolerance/
4. ("impaired fasting glucose" or "ifg").mp.
5. ("impaired glucose tolerance" or "itg").mp.
6. prediabet$.mp.
7. or/1-6
8. (de or dt or th).fs.
9. 7 and 8
10. exp Hypoglycemic Agents/tu [Therapeutic Use]
11. 7 and 10
12. 9 or 11
13. (200708$ or 200709$ or 20071$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed.
14. 12 and 13
15. limit 14 to "all adult (19 plus years)"
16. limit 15 to (english language and humans)
17. 16 not (case series or case reports or letter or editorial or comment).pt.

Cochrane Central Register of Controlled Trials January 2013
1. exp Diabetes Mellitus, Type 2/
2. Prediabetic State/
3. Glucose Intolerance/
4. ("impaired fasting glucose" or "ifg").mp.
5. ("impaired glucose tolerance" or "itg").mp.
6. prediabet$.mp.
7. or/1-6
8. (de or dt or th).fs.
9. 7 and 8
10. exp Hypoglycemic Agents/tu [Therapeutic Use]
11. 7 and 10
12. 9 or 11
13. Pregnancy/
14. 12 not 13
15. limit 14 to yr="2007 -Current"
16. limit 15 to medline records
17. 15 not 16

All KQs
Cochrane Database of Systematic Reviews 2005 to January 2013
1. diabetes mellitus.ti.
2. type 2 diabetes.ti.
3. (child$ or pediatri$ or adolescen$ or pregnan$).ti.
4. (1 or 2) not 3

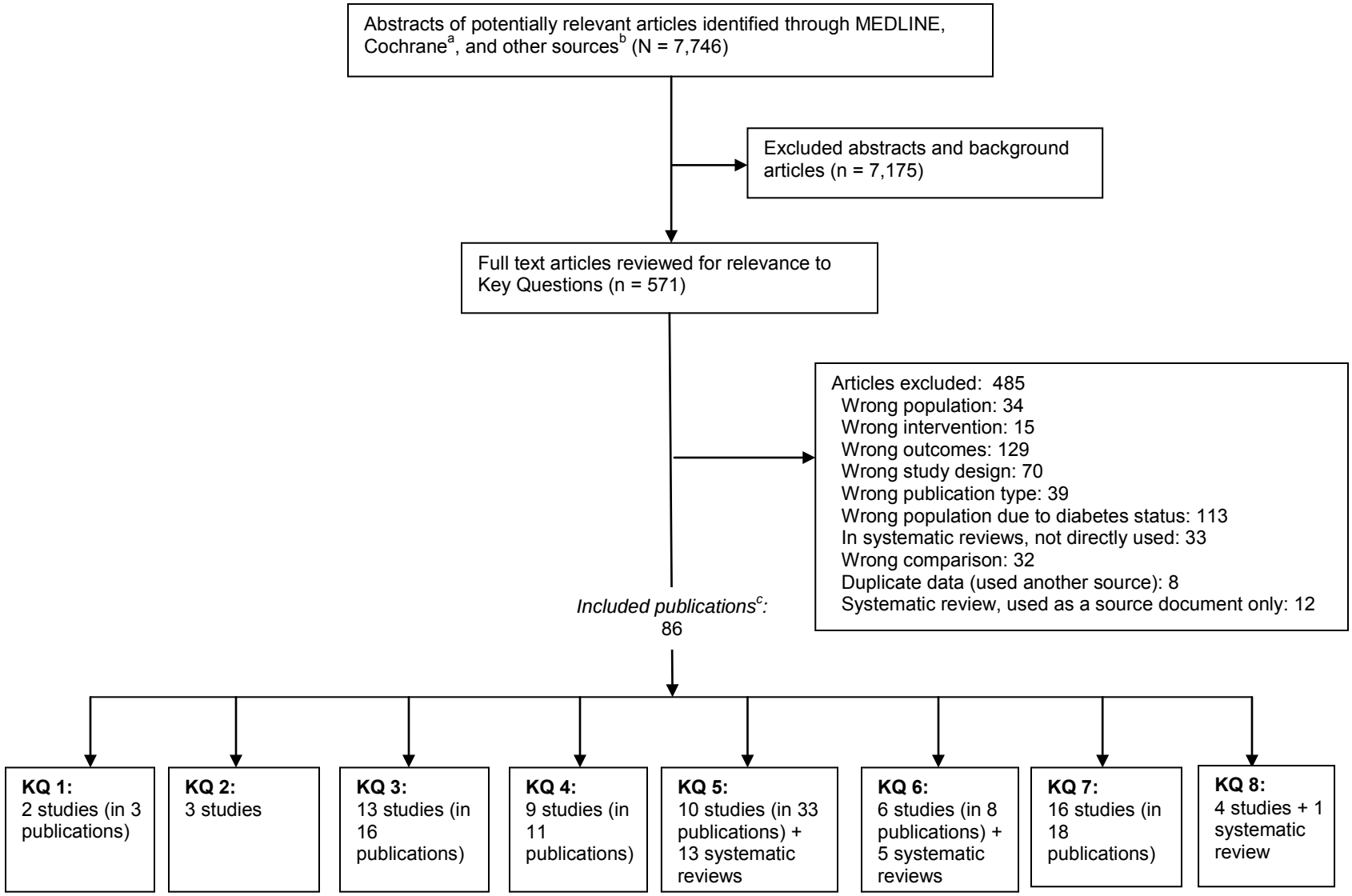
5. ("impaired fasting glucose" or "impaired glucose tolerance" or "ifg" or "itg" or "prediabete$").ti.
6. 4 or 5
7. limit 6 to protocols
8. 6 not 7

Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
Populations	**KQs 1, 2:** Asymptomatic, nonpregnant adults **KQs 3, 4:** Asymptomatic, nonpregnant adults with screen-detected or mild type 2 diabetes (based on untreated A1c levels), impaired fasting glucose, or impaired glucose tolerance **KQ 5:** Asymptomatic, nonpregnant adults with screen-detected or mild type 2 diabetes (based on untreated A1c levels), impaired fasting glucose, or impaired glucose tolerance, and also abnormal blood pressure and/or lipid levels **KQ 6:** Asymptomatic, nonpregnant adults with impaired fasting glucose or impaired glucose tolerance **KQ 7:** All of the above	**KQs 1–7:** Children, adolescents, pregnant women; individuals with symptomatic type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance
Interventions	**KQs 1, 2:** Screening (targeted or universal) for impaired fasting glucose, impaired glucose tolerance, or diabetes **KQs 3, 4, 6:** Any intervention for glycemic control; lifestyle modification **KQ 5:** Any intervention for more stringent blood pressure or lipid control or aspirin; more intensive lifestyle modification **KQ 7:** All of the above	
Comparison	**KQ 1:** No screening or alternative screening strategies **KQs 3, 4:** No intervention/usual care or interventions in individuals with advanced diabetes **KQ 5:** Conventional intervention **KQ 6:** No intervention or usual care **KQ 7:** All of the above	
Outcomes	**KQs 1, 3, 5:** Mortality, cardiovascular morbidity (including myocardial infarction, stroke, congestive heart failure), chronic kidney disease, amputations, skin ulcers, visual impairment including blindness, periodontitis including tooth loss, moderate-severe neuropathy, quality of life **KQ 2:** Labeling, anxiety, false-positive results **KQ 4:** Serious side effects from treatments, including death, heart attack, stroke, cancer, and hypoglycemic event requiring medical attention **KQ 6:** Development of type 2 diabetes **KQ 7:** All of the above	
Settings	**KQs 1–7:** Applicable to primary care	
Study Designs	**KQs 1, 3, 5, 6:** Randomized, controlled trials and controlled observational studies, systematic reviews **KQs 2:** Any **KQ 4:** Randomized, controlled trials and controlled observational studies, systematic reviews, and large longitudinal studies. KQ 7: All of the above	

Abbreviation: KQ = key question.

Appendix A3. Literature Flow Diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
[b] Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
[c] Some studies have multiple publications and some are included for more than one Key Question.

Wrong population

Aas AM, Ohrvik J, Malmberg K, Ryden L, Birkeland KI, Investigators D. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes Obes Metab*. 2009;11(4):323-9.

Ali M, White J, Lee C-H, Palmer JL, Smith-Palmer J, Fakhoury W, et al. Therapy conversion to biphasic insulin aspart 30 improves long-term outcomes and reduces the costs of type 2 diabetes in Saudi Arabia. *J Med Econ*. 2008;11(4):651-70.

Athyros VG, Ganotakis E, Kolovou GD, Nicolaou V, Achimastos A, Bilianou E, et al. Assessing the treatment effect in metabolic syndrome without perceptible diabetes (ATTEMPT): a prospective-randomized study in middle aged men and women. *Curr Vasc Pharmacol*. 2011;9(6):647-57.

Bayraktar S, Hernadez-Aya LF, Lei X, Meric-Bernstam F, Litton JK, Hsu L, et al. Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. *Cancer*. 2012;118(5):1202-11.

Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.

Bhatt DL, Chew DP, Grines C, Mukherjee D, Leesar M, Gilchrist IC, et al. Peroxisome proliferator–activated receptor γ agonists for the Prevention of Adverse events following percutaneous coronary Revascularization—results of the PPAR Study. *Am Heart J*. 2007;154(1):137-43.

Bilous R, Chaturvedi N, Sjolie AK, Fuller J, Klein R, Orchard T, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med*. 2009;151(1):11-20, W3-4.

Bo S, Ciccone G, Baldi C, Benini L, Dusio F, Forastiere G, et al. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. *J Gen Intern Med*. 2007;22(12):1695-703.

Burgess DC, Hunt D, Li L, Zannino D, Williamson E, Davis TM, et al. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Eur Heart J*. 2010;31(1):92-9.

Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study.[Erratum appears in *BMJ*. 2013;347:f4356]. *BMJ*. 2013;346:f2610.

Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371(9607):117-25.

Davidson MB, Raskin P, Tanenberg RJ, Vlajnic A, Hollander P. A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. *Endocr Pract*. 2011;17(3):395-403.

Du X, Ninomiya T, de Galan B, Abadir E, Chalmers J, Pillai A, et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J*. 2009;30(9):1128-35.

Duckworth WC, Abraira C, Moritz TE, Davis SN, Emanuele N, Goldman S, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications*. 2011;25(6):355-61.

Duran-Perez EG, Almeda-Valdes P, Cuevas-Ramos D, Campos-Barrera E, Munoz-Hernandez L, Gomez-Perez FJ. Treatment of metabolic syndrome slows progression of diabetic nephropathy. *Metab Syndr Relat Disord* 2011;9(6):483-9.

Graffy J, Grant J, Williams K, Cohn S, Macbay S, Griffin S, et al. More than measurement: practice team experiences of screening for type 2 diabetes. *Fam Pract*. 2010;27(4):386-94.

Hanefeld M, Karasik A, Koehler C, Westermeier T, Chiasson J-L. Metabolic syndrome and its single traits as risk factors for diabetes in people with impaired glucose tolerance: the STOP-NIDDM trial. *Diab Vasc Dis Res*. 2009;6(1):32-7.

Hermanns N, Kulzer B, Maier B, Mahr M, Haak T. The effect of an education programme (MEDIAS 2 ICT) involving intensive insulin treatment for people with type 2 diabetes. *Patient Educ Couns*. 2012;86(2):226-32.

James WPT, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-17.

Juul L, Sandbaek A, Foldspang A, Frydenberg M, Borch-Johnsen K, Lauritzen T. Adherence to guidelines in people with screen-detected type 2 diabetes, ADDITION, Denmark. *Scand J Prim Health Care*. 2009;27(4):223-31.

Kereiakes DJ, Petersen JL, Batchelor WB, Fitzgerald PJ, Mehran R, Lansky A, et al. Clinical and angiographic outcomes in diabetic patients following single or multivessel stenting in the COSTAR II randomized trial. *J Invasive Cardiol*. 2008;20(7):335-41.

Kjeldsen SE, McInnes GT, Mancia G, Hua TA, Julius S, Weber MA, et al. Progressive effects of valsartan compared with amlodipine in prevention of diabetes according to categories of diabetogenic risk in hypertensive patients: the VALUE trial. *Blood Press*. 2008;17(3):170-7.

Krane V, Heinrich F, Meesmann M, Olschewski M, Lilienthal J, Angermann C, et al. Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. *Clin J Am Soc Nephrol*. 2009;4(2):394-400.

Krane V, Winkler K, Drechsler C, Lilienthal J, Marz W, Wanner C, et al. Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis. *Kidney Int*. 2008;74(11):1461-7.

Lowe J, Linjawi S, Mensch M, James K, Attia J. Flexible eating and flexible insulin dosing in patients with diabetes: Results of an intensive self-management course. *Diabetes Res Clin Pract*. 2008;80(3):439-43.

Martinez-Martin FJ, Rodriguez-Rosas H, Peiro-Martinez I, Soriano-Perera P, Pedrianes-Martin P, Comi-Diaz C. Olmesartan/amlodipine vs olmesartan/hydrochlorothiazide in hypertensive patients with metabolic syndrome: the OLAS study. *J Hum Hypertens*. 2011;25(6):346-53.

Nieuwdorp M, Stroes ES, Kastelein JJ, Fenofibrate/Metformin Study G. Normalization of metabolic syndrome using fenofibrate, metformin or their combination. *Diabetes Obes Metab*. 2007;9(6):869-78.

Oh EG, Bang SY, Hyun SS, Kim SH, Chu SH, Jeon JY, et al. Effects of a 6-month lifestyle modification intervention on the cardiometabolic risk factors and health-related qualities of life in women with metabolic syndrome. *Metabolism.* 2010;59(7):1035-43.

Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. *J Am Coll Cardiol*. 2010;55(25):2878-86.

Rosenstock J, Klaff LJ, Schwartz S, Northrup J, Holcombe JH, Wilhelm K, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care*. 2010;33(6):1173-5.

Sargeant LA, Simmons RK, Barling RS, Butler R, Williams KM, Prevost AT, et al. Who attends a UK diabetes screening programme? Findings from the ADDITION-Cambridge study. *Diabet Med*. 2010;27(9):995-1003.

Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care*. 2009;32(3):493-8.

Singh S, Loke YK, Furberg CD. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis. *Thorax*. 2011;66(5):383-8.

Ting RD, Keech AC, Drury PL, Donoghoe MW, Hedley J, Jenkins AJ, et al. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD Study. *Diabetes Care*. 2012;35(2):218-25.

Wrong intervention

Cleveringa FGW, Welsing PMJ, van den Donk M, Gorter KJ, Niessen LW, Rutten GEHM, et al. Cost-effectiveness of the diabetes care protocol, a multifaceted computerized decision support diabetes management intervention that reduces cardiovascular risk. *Diabetes Care*. 2010;33(2):258-63.

Coronel F, Cigarran S, Herrero JA. Early initiation of peritoneal dialysis in diabetic patients. *Scand J Urol Nephrol*. 2009;43(2):148-53.

Grant SJ, Bensoussan A, Chang D, Kiat H, Klupp NL, Liu PJ, et al. Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database Syst Rev*. 2009(4).
Ip MS, Bressler SB, Antoszyk AN, Flaxel CJ, Kim JE, Friedman SM, et al. A

randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features. *Retina.* 2008;28(7):919-30.

Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*. 2011;34(4):828-37.

Kamoi K, Ito T, Miyakoshi M, Minagawa S. Usefulness of home blood pressure measurement in the morning in patients with type 2 diabetes: long-term results of a prospective longitudinal study. *Clin Exp Hypertens*. 2010;32(3):184-92.

Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ*. 2012;344:e1369.

Lievre MM, Moulin P, Thivolet C, Rodier M, Rigalleau V, Penfornis A, et al. Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. *Trials.* 2011;12:23.

Londahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabet Med*. 2011;28(2):186-90.

Nield L, Moore H, Hooper L, Cruickshank K, Vyas A, Whittaker V, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. *Cochrane Database Syst Rev*. 2009(1).

Nield L, Summerbell CD, Hooper L, Whittaker V, Moore H. Dietary advice for the prevention of type 2 diabetes mellitus in adults. *Cochrane Database Syst Rev*. 2008(3).

Ose D, Miksch A, Urban E, Natanzon I, Szecsenyi J, Kunz CU, et al. Health related quality of life and comorbidity. A descriptive analysis comparing EQ-5D dimensions of patients in the German disease management program for type 2 diabetes and patients in routine care. *BMC Health Serv Res*. 2011;11:179.

Ratner R, Han J, Nicewarner D, Yushmanova I, Hoogwerf BJ, Shen L. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. *Cardiovasc Diabetol*. 2011;10:22.

Ruggenenti P, Fassi A, Ilieva AP, Iliev IP, Chiurchiu C, Rubis N, et al. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. *J Hypertens*. 2011;29(2):207-16.

Wang C-C, Chen W-L, Kao T-W, Chang Y-W, Loh C-H, Chou C-C. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population.[Erratum appears in *Clin Ther*. 2012 Feb;34(2):508 Note: Chou, Chih-Chieh [corrected to Chou, Chin-Chieh]]. *Clin Ther*. 2011;33(12):1904-13.

Wrong outcomes

Abe H, Minatoguchi S, Ohashi H, Murata I, Minagawa T, Okuma T, et al. Renoprotective effect of the addition of losartan to ongoing treatment with an

angiotensin converting enzyme inhibitor in type-2 diabetic patients with nephropathy. *Hypertens Res*. 2007;30(10):929-35.

Adachi M, Yamaoka K, Watanabe M, Nishikawa M, Hida E, Kobayashi I, et al. Effects of lifestyle education program for type 2 diabetes patients in clinics: study design of a cluster randomized trial. *BMC Public Health*. 2010;10:742.

Adarkwah CC, Gandjour A. Cost-effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in newly diagnosed type 2 diabetes in Germany. *Int J Technol Assess Health Care*. 2010;26(1):62-70.

Afzali HHA, Karnon J, Gray J, Beilby J. A model-based evaluation of collaborative care in management of patients with type 2 diabetes in Australia: an initial report. *Aust Health Rev*. 2012;36(3):258-63.

Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL, McElnay JC. Influence of pharmaceutical care on health outcomes in patients with Type 2 diabetes mellitus. *Br J Clin Pharmacol*. 2009;67(5):547-57.

Allen P, Thompson JL, Herman CJ, Whyte AN, Wolfe VK, Qualls C, et al. Impact of periodic follow-up testing among urban American Indian women with impaired fasting glucose. *Prev Chronic Dis*. 2008;5(3):A76.

Alvarsson M, Sundkvist G, Lager I, Berntorp K, Fernqvist-Forbes E, Steen L, et al. Effects of insulin vs. glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up. *Diabetes Obes Metab*. 2008;10(5):421-9.

Alvear-Galindo MG, Laurell AC. [Analysis of the diabetes mellitus screening program in the Federal District, Mexico]. *Cad Saude Publica*. 2010;26(2):299-310.

Andersson U, Berger K, Hogberg A, Landin-Olsson M, Holm C. Effects of rose hip intake on risk markers of type 2 diabetes and cardiovascular disease: a randomized, double-blind, cross-over investigation in obese persons. *Eur J Clin Nutr*. 2012;66(5):585-90.

Askew DA, Jackson CL, Ware RS, Russell A. Protocol and baseline data from The Inala Chronic Disease Management Service evaluation study: a health services intervention study for diabetes care. *BMC Health Serv Res*. 2010;10:134.

Athyros VG, Elisaf MS, Alexandrides T, Achimastos A, Ganotakis E, Bilianou E, et al. Long-term impact of multifactorial treatment on new-onset diabetes and related cardiovascular events in metabolic syndrome: a post hoc ATTEMPT analysis. *Angiology*. 2012;63(5):358-66.

Aujla N, Skinner TC, Khunti K, Davies MJ. The prevalence of depressive symptoms in a white European and South Asian population with impaired glucose regulation and screen-detected Type 2 diabetes mellitus: a comparison of two screening tools. *Diabet Med*. 2010;27(8):896-905.

Bakris GL, Toto RD, McCullough PA, Rocha R, Purkayastha D, Davis P, et al. Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. *Kidney Int*. 2008;73(11):1303-9.

Balkau B, Bouee S, Avignon A, Verges B, Chartier I, Amelineau E, et al. Type 2 diabetes treatment intensification in general

practice in France in 2008-2009: the DIAttitude Study. *Diabetes Metab*. 2012;38 Suppl 3:S29-35.

Balkrishnan R, Arondekar BV, Camacho FT, Shenolikar RA, Horblyuk R, Anderson RT. Comparisons of rosiglitazone versus pioglitazone monotherapy introduction and associated health care utilization in medicaid-enrolled patients with type 2 diabetes mellitus. *Clin Ther*. 2007;29 Spec No:1306-15.

Bayliss EA, Blatchford PJ, Newcomer SR, Steiner JF, Fairclough DL. The effect of incident cancer, depression and pulmonary disease exacerbations on type 2 diabetes control. *J Gen Intern Med*. 2011;26(6):575-81.

Bek T, Lund-Andersen H, Hansen AB, Johnsen KB, Sandbaek A, Lauritzen T. The prevalence of diabetic retinopathy in patients with screen-detected type 2 diabetes in Denmark: the ADDITION study. *Acta Ophthalmol (Oxf)*. 2009;87(3):270-4.

Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. *Diabetologia*. 2010;53(5):875-81.

Beyazit E, Mollaoglu M. Investigation of effect on glycosylated hemoglobin, blood pressure, and body mass index of diabetes intensive education program in patients with type 2 diabetes mellitus. *Am J Mens Health*. 2011;5(4):351-7.

Black. Change in cardiovascular risk factors following early diagnosis of type 2 diabetes. . In press.

Black JA, Sharp SJ, Wareham NJ, Sandbæk A, Rutten GEHM, Lauritzen T, et al. Does early intensive multifactorial therapy reduce modelled cardiovascular risk in individuals with screen-detected diabetes? Results from the ADDITION-Europe cluster randomized trial. *Diabet Med*. 2014:n/a-n/a.

Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*. 2008;31(11):2086-91.

Bonds DE, Craven TE, Buse J, Crouse JR, Cuddihy R, Elam M, et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. *Diabetologia*. 2012;55(6):1641-50.

Bouchard DR, Baillargeon J-P, Gagnon C, Brown C, Langlois M-F. Impact of health professionals' contact frequency on response to a lifestyle intervention with individuals at high risk for diabetes. *Diabetes Res Clin Pract*. 2012;96(2):129-34.

Brouwer BG, Visseren FLJ, Algra A, van Bockel JH, Bollen ELEM, Doevendans PA, et al. Effectiveness of a hospital-based vascular screening programme (SMART) for risk factor management in patients with established vascular disease or type 2 diabetes: a parallel-group comparative study. *J Intern Med*. 2010;268(1):83-93.

Bulcao C, Ribeiro-Filho FF, Sanudo A, Roberta Ferreira SG. Effects of simvastatin and metformin on inflammation and insulin resistance in individuals with mild metabolic syndrome. *Am J Cardiovasc Drugs*. 2007;7(3):219-24.

Chakreeyarat S, Saetung S, Chailurkit L-o, Rattanasiri S, Ditbanjong S, Chitrapazt N, et al. Elevated vitamin D status in postmenopausal women on thiazolidinediones for type 2 diabetes. *Endocrine*. 2011;39(3):278-82.

Chalmers J, Hunter JE, Robertson SJ, Baird J, Martin M, Franks CI, et al. Effects of early use of pioglitazone in combination with metformin in patients with newly diagnosed type 2 diabetes. *Curr Med Res Opin*. 2007;23(8):1775-81.

Chalmers J, Kengne A-P, Joshi R, Perkovic V, Patel A. New insights from ADVANCE. Journal of Hypertension - Supplement. 2007;25(1):S23-30.

Chamnan P, Simmons RK, Khaw KT, Wareham NJ, Griffin SJ. Estimating the population impact of screening strategies for identifying and treating people at high risk of cardiovascular disease: modelling study. *BMJ*. 2010;340:c1693.

Chao T-F, Leu H-B, Huang C-C, Chen J-W, Chan W-L, Lin S-J, et al. Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. *Int J Cardiol*. 2012;156(2):199-202.

Charbonnel B, DeFronzo R, Davidson J, Schmitz O, Birkeland K, Pirags V, et al. Pioglitazone use in combination with insulin in the prospective pioglitazone clinical trial in macrovascular events study (PROactive19). *J Clin Endocrinol Metab*. 2010;95(5):2163-71.

Charles M, Fleischer J, Witte DR, Ejskjaer N, Borch-Johnsen K, Lauritzen T, et al. Impact of early detection and treatment of diabetes on the 6-year prevalence of cardiac autonomic neuropathy in people with screen-detected diabetes: ADDITION-Denmark, a cluster-randomised study. *Diabetologia*. 2013;56(1):101-8.

Chatterjee R, Narayan KMV, Lipscomb J, Phillips LS. Screening adults for pre-diabetes and diabetes may be cost-saving. *Diabetes Care*. 2010;33(7):1484-90.

Chon S, Oh S, Kim SW, Kim J-W, Kim YS, Woo J-t. The effect of early insulin therapy on pancreatic -cell function and long-term glycemic control in newly diagnosed type 2 diabetic patients. *Korean J Intern Med*. 2010;25(3):273-81.

Ciardullo AV, Daghio MM, Bevini M, Feltri G, Novi D, Fattori G, et al. Joint and distinct risk factors associated with micro- and macrovascular complications in a cohort of type 2 diabetic patients cared through disease management. *Acta Diabetol*. 2010;47(4):301-8.

Coclami T, Cross M. Psychiatric co-morbidity with type 1 and type 2 diabetes mellitus. *East Mediterr Health J*. 2011;17(10):777-83.

Colagiuri S, Walker AE. Using an economic model of diabetes to evaluate prevention and care strategies in Australia. *Health Aff (Millwood)*. 2008;27(1):256-68.

Cooper GJS, Young AA, Gamble GD, Occleshaw CJ, Dissanayake AM, Cowan BR, et al. A copper(II)-selective chelator ameliorates left-ventricular hypertrophy in type 2 diabetic patients: a randomised placebo-controlled study. *Diabetologia*. 2009;52(4):715-22.

Cosson E, Nguyen MT, Hamo-Tchatchouang E, Banu I, Chiheb S, Charnaux N, et al. What would be the outcome if the American Diabetes

Association recommendations of 2010 had been followed in our practice in 1998-2006? *Diabet Med*. 2011;28(5):567-74.

Covington P, Christopher R, Davenport M, Fleck P, Mekki QA, Wann ER, et al. Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor alogliptin: a randomized, double-blind, placebo-controlled, multiple-dose study in adult patients with type 2 diabetes. *Clin Ther*. 2008;30(3):499-512.

Dalsgaard EM, Lauritzen T, Christiansen T, Mai KS, Borch-Johnsen K, Sandbaek A. Socioeconomic factors related to attendance at a Type 2 diabetes screening programme. *Diabet Med*. 2009;26(5):518-25.

Dalsgaard E-M, Christensen JO, Skriver MV, Borch-Johnsen K, Lauritzen T, Sandbaek A. Comparison of different stepwise screening strategies for type 2 diabetes: Finding from Danish general practice, Addition-DK. *Prim Care Diabetes*. 2010;4(4):223-9.

Davidson JA, Lacaya LB, Jiang H, Heilmann CR, Scism-Bacon JL, Gates JR, et al. Impact of race/ethnicity on the efficacy and safety of commonly used insulin regimens: a post hoc analysis of clinical trials in type 2 diabetes mellitus. *Endocr Pract*. 2010;16(5):818-28.

Doucet J, Chacra A, Maheux P, Lu J, Harris S, Rosenstock J. Efficacy and safety of saxagliptin in older patients with type 2 diabetes mellitus. *Curr Med Res Opin*. 2011;27(4):863-9.

Dunkley AJ, Davies MJ, Stone MA, Taub NA, Troughton J, Yates T, et al. The Reversal Intervention for Metabolic Syndrome (TRIMS) study: rationale, design, and baseline data. *Trials*. 2011;12:107.

Eborall H, Davies R, Kinmonth A-L, Griffin S, Lawton J. Patients' experiences of screening for type 2 diabetes: prospective qualitative study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ*. 2007;335(7618):490.

Fakhoury WKH, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. *Pharmacology*. 2010;86(1):44-57.

Feldman L, Shani M, Efrati S, Beberashvili I, Baevsky T, Weissgarten J, et al. Association between rosiglitazone use and decline in renal function in patients with type 2 diabetes mellitus. *J Nephrol*. 2010;23(3):350-6.

Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. *Diabet Med*. 2010;27(12):1409-19.

Giorda CB, Avogaro A, Maggini M, Lombardo F, Mannucci E, Turco S, et al. Recurrence of cardiovascular events in patients with type 2 diabetes: epidemiology and risk factors. *Diabetes Care*. 2008;31(11):2154-9.

Goldberg RB, Temprosa M, Haffner S, Orchard TJ, Ratner RE, Fowler SE, et al. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: the Diabetes Prevention Program randomized trial by the

Diabetes Prevention Program Research Group. *Diabetes Care*. 2009;32(4):726-32.

Goyder E, Wild S, Fischbacher C, Carlisle J, Peters J. Evaluating the impact of a national pilot screening programme for type 2 diabetes in deprived areas of England. *Fam Pract*. 2008;25(5):370-5.

Hanefeld M, Herman GA, Wu M, Mickel C, Sanchez M, Stein PP, et al. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. *Curr Med Res Opin*. 2007;23(6):1329-39.

Hare JL, Hordern MD, Leano R, Stanton T, Prins JB, Marwick TH. Application of an exercise intervention on the evolution of diastolic dysfunction in patients with diabetes mellitus: efficacy and effectiveness. *Circ Heart Fail*. 2011;4(4):441-9.

Hartmann M, Kopf S, Kircher C, Faude-Lang V, Djuric Z, Augstein F, et al. Sustained effects of a mindfulness-based stress-reduction intervention in type 2 diabetic patients: design and first results of a randomized controlled trial (the Heidelberger Diabetes and Stress-study). *Diabetes Care*. 2012;35(5):945-7.

Huisman S, de Gucht V, Maes S, Schroevers M, Chatrou M, Haak H. Self-regulation and weight reduction in patients with type 2 diabetes: a pilot intervention study. *Patient Educ Couns*. 2009;75(1):84-90.

Ikeda H, Hamamoto Y, Honjo S, Nabe K, Wada Y, Koshiyama H. Olmesartan reduced microalbuminuria in Japanese subjects with type 2 diabetes. *Diabetes Res Clin Pract*. 2009;83(1):117-8.

Investigators AES, Group AC. Effects of perindopril-indapamide on left ventricular diastolic function and mass in patients with type 2 diabetes: the ADVANCE Echocardiography Substudy. *J Hypertens*. 2011;29(7):1439-47.

Investigators DT. Incidence of diabetes following ramipril or rosiglitazone withdrawal. *Diabetes Care*. 2011;34(6):1265-9.

Iwamoto Y, Taniguchi T, Nonaka K, Okamoto T, Okuyama K, Arjona Ferreira JC, et al. Dose-ranging efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. *Endocr J*. 2010;57(5):383-94.

Janssen PGH, Gorter KJ, Stolk RP, Akarsubasi M, Rutten GEHM. Three years follow-up of screen-detected diabetic and non-diabetic subjects: who is better off? The ADDITION Netherlands study. *BMC Fam Pract*. 2008;9:67.

Janssen PGH, Gorter KJ, Stolk RP, Rutten GEHM. Low yield of population-based screening for Type 2 diabetes in the Netherlands: the ADDITION Netherlands study. *Fam Pract*. 2007;24(6):555-61.

Johansen NB, Charles M, Vistisen D, Rasmussen SS, Wiinberg N, Borch-Johnsen K, et al. Effect of intensive multifactorial treatment compared with routine care on aortic stiffness and central blood pressure among individuals with screen-detected type 2 diabetes: the ADDITION-Denmark study. *Diabetes Care*. 2012;35(11):2207-14.

Kamber N, Davis WA, Bruce DG, Davis TME. Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. *Med J Aust*. 2008;188(8):446-9.

Katula JA, Vitolins MZ, Rosenberger EL, Blackwell CS, Morgan TM, Lawlor MS, et al. One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project.[Erratum appears in Diabetes Care. 2012 Feb;35(2):455]. *Diabetes Care*. 2011;34(7):1451-7.

Kawamori R, Inagaki N, Araki E, Watada H, Hayashi N, Horie Y, et al. Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. *Diabetes Obes Metab*. 2012;14(4):348-57.

Ke B, Shi L, Jun-jie Z, Chen D-s, Meng J, Qin J. Protective effects of modified linggui zhugan decoction combined with short-term very low calorie diets on cardiovascular risk factors in obese patients with impaired glucose tolerance. *J Tradit Chin Med*. 2012;32(2):193-8.

Kellar I, Mann E, Kinmonth AL, Prevost AT, Sutton S, Marteau TM. Can informed choice invitations lead to inequities in intentions to make lifestyle changes among participants in a primary care diabetes screening programme? Evidence from a randomized trial. Public Health. 2011;125(9):645-52.

Kelley DS, Adkins Y, Woodhouse LR, Swislocki A, Mackey BE, Siegel D. Docosahexaenoic acid supplementation improved lipocentric but not glucocentric markers of insulin sensitivity in hypertriglyceridemic men. *Metab Syndr Relat Disord* 2012;10(1):32-8.

Kerr JL, Timpe EM, Petkewicz KA. Bromocriptine mesylate for glycemic management in type 2 diabetes mellitus. *Ann Pharmacother*. 2010;44(11):1777-85.

Khowaja K, Waheed H. Self-glucose monitoring and glycaemic control at a tertiary care university hospital, Karachi, Pakistan. JPMA - Journal of the Pakistan Medical Association. 2010;60(12):1035-8.

Kikuchi M, Abe N, Kato M, Terao S, Mimori N, Tachibana H. Vildagliptin dose-dependently improves glycemic control in Japanese patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2009;83(2):233-40.

Kim CS, Park SY, Kang JG, Lee SJ, Ihm SH, Choi MG, et al. Insulin dose titration system in diabetes patients using a short messaging service automatically produced by a knowledge matrix. *Diabetes Technol Ther*. 2010;12(8):663-9.

Kim HJ, Park KS, Lee SK, Min KW, Han KA, Kim YK, et al. Effects of pinitol on glycemic control, insulin resistance and adipocytokine levels in patients with type 2 diabetes mellitus. *Ann Nutr Metab*. 2012;60(1):1-5.

Kim MK, Ko S-H, Baek K-H, Ahn Y-B, Yoon K-H, Kang M-I, et al. Long-term effects of rosiglitazone on the progressive decline in renal function in patients with type 2 diabetes. *Korean J Intern Med*. 2009;24(3):227-32.

Kim S-I, Kim H-S. Effectiveness of mobile and internet intervention in patients with obese type 2 diabetes. *Int J Med Inf*. 2008;77(6):399-404.

King AB, Wolfe GS. Evaluation of a diabetes specialist-guided primary care

diabetes treatment program. *J Am Acad Nurse Pract*. 2009;21(1):24-30.

Kipnes MS, Hollander P, Fujioka K, Gantz I, Seck T, Erondu N, et al. A one-year study to assess the safety and efficacy of the CB1R inverse agonist taranabant in overweight and obese patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(6):517-31.

Klein Woolthuis EP, de Grauw WJC, van Gerwen WHEM, van den Hoogen HJM, van de Lisdonk EH, Metsemakers JFM, et al. Yield of opportunistic targeted screening for type 2 diabetes in primary care: the diabscreen study. *Ann Fam Med*. 2009;7(5):422-30.

Koekkoek PS, Ruis C, van den Donk M, Biessels GJ, Gorter KJ, Kappelle LJ, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-Netherlands study: a cluster-randomized trial. *J Neurol Sci*. 2012;314(1-2):71-7.

Kosuri M, Sridhar GR. Yoga practice in diabetes improves physical and psychological outcomes. *Metab Syndr Relat Disord* 2009;7(6):515-7.

Lambers S, Van Laethem C, Van Acker K, Calders P. Influence of combined exercise training on indices of obesity, diabetes and cardiovascular risk in type 2 diabetes patients. *Clin Rehabil*. 2008;22(6):483-92.

Lazo M, Solga SF, Horska A, Bonekamp S, Diehl AM, Brancati FL, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care*. 2010;33(10):2156-63.

Lundby Christensen L, Almdal T, Boesgaard T, Breum L, Dunn E, Gade-Rasmussen B, et al. Study rationale and design of the CIMT trial: the Copenhagen Insulin and Metformin Therapy trial. *Diabetes Obes Metab*. 2009;11(4):315-22.

Mai KS, Sandbaek A, Borch-Johnsen K, Lauritzen T. Are lifestyle changes achieved after participation in a screening programme for Type 2 diabetes? The ADDITION Study, Denmark. *Diabet Med*. 2007;24(10):1121-8.

Maindal HT, Sandbaek A, Kirkevold M, Lauritzen T. Effect on motivation, perceived competence, and activation after participation in the "Ready to Act" programme for people with screen-detected dysglycaemia: a 1-year randomised controlled trial, Addition-DK. *Scand J Public Health*. 2011;39(3):262-71.

Malanda UL, Welschen MCL, Riphagen II, Dekker JM, Nijpels G, Bot DMS. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. *Cochrane Database Syst Rev*. 2012(5).

Malin SK, Nightingale J, Choi SE, Chipkin SR, Braun B. Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults. *Obesity (Silver Spring).* 2013;21(1):93-100.

Memişoğullari R, Akçay F, Coşkun A, Korkmaz U. Comparison of Gliclazide Treatment with Diet Therapy on Acute Phase Protein Levels in Patients with Type 2 Diabetes. *Turk J Med Sci* 2009;39(1):73-6.

Mychaleckyj JC, Craven T, Nayak U, Buse J, Crouse JR, Elam M, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic

participants. *Diabetes Care*. 2012;35(5):1008-14.

Norris SL, Zhang X, Avenell A, Gregg E, Brown T, Schmid CH, et al. Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(1).

Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Long-term non-pharmacological weight loss interventions for adults with prediabetes. *Cochrane Database Syst Rev*. 2009(1).

Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(3).

Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, et al. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. *J Atheroscler Thromb*. 2010;17(8):828-33.

Perreault L, Kahn SE, Christophi CA, Knowler WC, Hamman RF, Diabetes Prevention Program Research G. Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care*. 2009;32(9):1583-8.

Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE, et al. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. *Lancet*. 2012;379(9833):2243-51.

Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care*. 2010;33(7):1578-84.

Preiss D, Giles TD, Thomas LE, Sun J-L, Haffner SM, Holman RR, et al. Predictors of stroke in patients with impaired glucose tolerance: results from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial. ***Stroke.*** 2013;44(9):2590-3.

Raisch DW, Feeney P, Goff DC, Jr., Narayan KMV, O'Connor PJ, Zhang P, et al. Baseline comparison of three health utility measures and the feeling thermometer among participants in the Action to Control Cardiovascular Risk in Diabetes trial. *Cardiovasc Diabetol*. 2012;11:35.

Rasmussen SS, Glumer C, Sandbaek A, Lauritzen T, Borch-Johnsen K. Determinants of progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screened population: 3 year follow-up in the ADDITION study, Denmark. *Diabetologia*. 2008;51(2):249-57.

Rasmussen SS, Glumer C, Sandbaek A, Lauritzen T, Carstensen B, Borch-Johnsen K. Short-term reproducibility of impaired fasting glycaemia, impaired glucose tolerance and diabetes The ADDITION study, DK. *Diabetes Res Clin Pract*. 2008;80(1):146-52.

Redmon JB, Bertoni AG, Connelly S, Feeney PA, Glasser SP, Glick H, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care*. 2010;33(6):1153-8.

Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med*. 2012;366(13):1209-17.

Renders MC, Valk GD, Griffin SJ, Wagner E, van Eijk TJ, Assendelft JJW. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *Cochrane Database Syst Rev*. 2009(1).

Retnakaran R, Qi Y, Harris SB, Hanley AJ, Zinman B. Changes over time in glycemic control, insulin sensitivity, and beta-cell function in response to low-dose metformin and thiazolidinedione combination therapy in patients with impaired glucose tolerance. *Diabetes Care*. 2011;34(7):1601-4.

Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(1).

Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(3).

Roman MJ, Howard BV, Howard WJ, Mete M, Fleg JL, Lee ET, et al. Differential impacts of blood pressure and lipid lowering on regression of ventricular and arterial mass: the Stop Atherosclerosis in Native Diabetics Trial. Hypertension. 2011;58(3):367-71.

Rosenstock J, Fonseca VA, Garvey WT, Goldberg RB, Handelsman Y, Abby SL, et al. Initial combination therapy with metformin and colesevelam for achievement of glycemic and lipid goals in early type 2 diabetes. *Endocr Pract*. 2010;16(4):629-40.

Rubak S, Sandbaek A, Lauritzen T, Borch-Johnsen K, Christensen B. Effect of "motivational interviewing" on quality of care measures in screen detected type 2 diabetes patients: a one-year follow-up of an RCT, ADDITION Denmark. *Scand J Prim Health Care*. 2011;29(2):92-8.

Rytter E, Vessby B, Asgard R, Ersson C, Moussavian S, Sjodin A, et al. Supplementation with a combination of antioxidants does not affect glycaemic control, oxidative stress or inflammation in type 2 diabetes subjects. *Free Radic Res*. 2010;44(12):1445-53.

Sabherwal S, Bravis V, Devendra D. Effect of oral vitamin D and calcium replacement on glycaemic control in South Asian patients with type 2 diabetes. *Int J Clin Pract*. 2010;64(8):1084-9.

Sacks FM. After the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: implications for fenofibrate. *Am J Cardiol*. 2008;102(12A):34L-40L.

Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roque i Figuls M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(1).

Safaei H, Janghorbani M, Aminorroaya A, Amini M. Lovastatin effects on bone mineral density in postmenopausal women with type 2 diabetes mellitus. *Acta Diabetol*. 2007;44(2):76-82.

Salinero-Fort MA, Carrillo-de Santa Pau E, Arrieta-Blanco FJ, Abanades-Herranz JC, Martin-Madrazo C, Rodes-Soldevila B, et al. Effectiveness of PRECEDE model for health education on changes and level of control of HbA1c, blood pressure, lipids,

and body mass index in patients with type 2 diabetes mellitus. *BMC Public Health*. 2011;11:267.

Samaropoulos XF, Light L, Ambrosius WT, Marcovina SM, Probstfield J, Jr DCG. The effect of intensive risk factor management in type 2 diabetes on inflammatory biomarkers. *Diabetes Res Clin Pract*. 2012;95(3):389-98.

Sandbaek A, Griffin SJ, Rutten G, Davies M, Stolk R, Khunti K, et al. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia*. 2008;51(7):1127-34.

Service FJ, Daube JR, O'Brien PC, Zimmerman BR, Swanson CJ, Brennan MD, et al. Effect of blood glucose control on peripheral nerve function in diabetic patients. *Mayo Clin Proc*. 1983;58(5):283-9.

Sridharan K, Mohan R, Ramaratnam S, Panneerselvam D. Ayurvedic treatments for diabetes mellitus. *Cochrane Database Syst Rev*. 2011(12):CD008288.

Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in "real-world" settings: an empowerment-based intervention. *Patient Educ Couns*. 2010;79(2):178-84.

Thomas D, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(1).

Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, et al. Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. *Diabetes Care*. 2007;30(11):2832-7.

van den Donk M, Sandbaek A, Borch-Johnsen K, Lauritzen T, Simmons RK, Wareham NJ, et al. Screening for type 2 diabetes. Lessons from the ADDITION-Europe study. *Diabet Med*. 2011;28(11):1416-24.

Wang W, Bu R, Su Q, Liu J, Ning G. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naive to oral antidiabetes therapy. *Expert Opin Pharmacother*. 2011;12(18):2791-9.

Webb DR, Khunti K, Gray LJ, Srinivasan BT, Farooqi A, Wareham N, et al. Intensive multifactorial intervention improves modelled coronary heart disease risk in screen-detected Type 2 diabetes mellitus: a cluster randomized controlled trial. *Diabet Med*. 2012;29(4):531-40.

Weber MB, Ranjani H, Meyers GC, Mohan V, Narayan KMV. A model of translational research for diabetes prevention in low and middle-income countries: The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial. *Prim Care Diabetes*. 2012;6(1):3-9.

Yeung VTF, Lee KF, Chan SH, Ho LF, Leung SK, Wong HY, et al. MicroAlbuminuria Prevalence Study (MAPS) in hypertensive type 2 diabetic patients in Hong Kong. *Hong Kong Med J.* 2006;12(3):185-90.

Wrong study design for Key Question

Anand SS, Dagenais GR, Mohan V, Diaz R, Probstfield J, Freeman R, et al. Glucose levels are associated with cardiovascular disease and death in an international cohort of normal glycaemic and dysglycaemic men and women: the EpiDREAM cohort study. *Eur J Prev Cardiolog*. 2012;19(4):755-64.

Aujla N, Davies MJ, Skinner TC, Gray LJ, Webb DR, Srinivasan B, et al. The association between anxiety and measures of glycaemia in a population-based diabetes screening programme. *Diabet Med*. 2011;28(7):785-8.

Banerjee S, Ghosh US, Dutta S. Clinicopathological profile of hepatic involvement in type-2 diabetes mellitus and its significance. *J Assoc Physicians India*. 2008;56:593-9.

Bartram S, Rigby D. Diabetes screening as part of a vascular disease risk management programme. *Community Pract*. 2012;85(10):24-7.

Baur DM, Klotsche J, Hamnvik O-PR, Sievers C, Pieper L, Wittchen H-U, et al. Type 2 diabetes mellitus and medications for type 2 diabetes mellitus are associated with risk for and mortality from cancer in a German primary care cohort. *Metabolism.* 2011;60(10):1363-71.

Bazelier MT, Vestergaard P, Gallagher AM, van Staa T-P, Cooper C, Leufkens HGM, et al. Risk of fracture with thiazolidinediones: disease or drugs? *Calcif Tissue Int*. 2012;90(6):450-7.

Beever R. The effects of repeated thermal therapy on quality of life in patients with type II diabetes mellitus. *J Altern Complement Med*. 2010;16(6):677-81.

Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of Type 2 diabetes: a systematic review. *Diabet Med*. 2007;24(4):333-43.

Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). *Pharmacoepidemiol Drug Saf*. 2010;19(7):715-21.

Brown SH, Abdelhafiz AH. Trials Review. *Postgrad Med*. 2009;121(5).

Buyken AE, von Eckardstein A, Schulte H, Cullen P, Assmann G. Type 2 diabetes mellitus and risk of coronary heart disease: results of the 10-year follow-up of the PROCAM study. *Eur J Cardiovasc Prev Rehabil*. 2007;14(2):230-6.

Carlsson LMS, Peltonen M, Ahlin S, Anveden A, Bouchard C, Carlsson B, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med*. 2012;367(8):695-704.

Chamnan P, Simmons RK, Khaw KT, Wareham NJ, Griffin SJ. Estimating the potential population impact of stepwise screening strategies for identifying and treating individuals at high risk of Type 2 diabetes: a modelling study. *Diabet Med*. 2012;29(7):893-904.

Chamnan P, Simmons RK, Khaw KT, Wareham NJ, Griffin SJ. Change in HbA1c over 3 years does not improve the prediction of cardiovascular disease over and above HbA1c measured at a single time point. *Diabetologia*. 2013;56(5):1004-11.

Chan S-P, Ji L-N, Nitiyanant W, Baik SH, Sheu WHH. Hypoglycemic symptoms in patients with type 2 diabetes in Asia-Pacific-Real-life effectiveness and care patterns of diabetes management: the RECAP-DM study. *Diabetes Res Clin Pract*. 2010;89(2):e30-2.

Charles M, Simmons RK, Williams KM, Roglic G, Sharp SJ, Kinmonth A-L, et al. Cardiovascular risk reduction following

diagnosis of diabetes by screening: 1-year results from the ADDITION-Cambridge trial cohort. Br J Gen Pract. 2012;62(599):e396-402.

Charlton J, Latinovic R, Gulliford MC. Explaining the decline in early mortality in men and women with type 2 diabetes: a population-based cohort study. *Diabetes Care*. 2008;31(9):1761-6.

Choi SH, Kim TH, Lim S, Park KS, Jang HC, Cho NH. Hemoglobin A1c as a diagnostic tool for diabetes screening and new-onset diabetes prediction: a 6-year community-based prospective study. *Diabetes Care*. 2011;34(4):944-9.

Chung YW, Han DS, Park KH, Eun CS, Yoo K-S, Park CK. Insulin therapy and colorectal adenoma risk among patients with Type 2 diabetes mellitus: a case-control study in Korea. *Dis Colon Rectum*. 2008;51(5):593-7.

Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA*. 2010;304(1):61-8.

Davila EP, Florez H, Trepka MJ, Fleming LE, Niyonsenga T, Lee DJ, et al. Strict glycemic control and mortality risk among US adults with type 2 diabetes. *J Diabetes Complications*. 2011;25(5):289-91.

Drury PL, Ting R, Zannino D, Ehnholm C, Flack J, Whiting M, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia*. 2011;54(1):32-43.

Echouffo-Tcheugui JB, Sargeant LA, Prevost AT, Williams KM, Barling RS, Butler R, et al. How much might cardiovascular disease risk be reduced by intensive therapy in people with screen-detected diabetes? *Diabet Med*. 2008;25(12):1433-9.

Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Nunez L, Gudbjornsdottir S, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia*. 2009;52(1):65-73.

Florez H, Luo J, Castillo-Florez S, Mitsi G, Hanna J, Tamariz L, et al. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. *Postgrad Med*. 2010;122(2):112-20.

Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med*. 2010;122(3):16-27.

Geiss LS, James C, Gregg EW, Albright A, Williamson DF, Cowie CC. Diabetes Risk Reduction Behaviors Among U.S. Adults with Prediabetes. *Am J Prev Med*. 2010;38(4):403-9.

Goz F, Karaoz S, Goz M, Ekiz S, Cetin I. Effects of the diabetic patients' perceived social support on their quality-of-life. *J Clin Nurs*. 2007;16(7):1353-60.

Green AJ, Fox KM, Grandy S, Group SS. Self-reported hypoglycemia and impact on

quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;96(3):313-8.

Grimley Evans J, Areosa Sastre A. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009(1).

Guerrero-Romero F, Rodriguez-Moran M. [Validation of an instrument for screening cases of type 2 diabetes and monitoring at-risk individuals in Mexico]. *Rev Panam Salud Publica*. 2010;27(3):181-6.

Habib ZA, Tzogias L, Havstad SL, Wells K, Divine G, Lanfear DE, et al. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. Pharmacoepidemiol *Drug Saf*. 2009;18(6):437-47.

Hu Y, Liu W, Chen Y, Zhang M, Wang L, Zhou H, et al. Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. *Acta Diabetol*. 2010;47(3):231-6.

Hung AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. *Kidney Int*. 2012;81(7):698-706.

Ilanne-Parikka P, Laaksonen DE, Eriksson JG, Lakka TA, Lindstr J, Peltonen M, et al. Leisure-time physical activity and the metabolic syndrome in the Finnish diabetes prevention study. *Diabetes Care*. 2010;33(7):1610-7.

Janka HU, Hessel F, Walzer S, Ma Ller E. Insulin glargine added to therapy with oral antidiabetic agents improves glycemic control and reduces long-term complications in patients with type 2 diabetes - a simulation with the Diabetes Mellitus Model (DMM). *Int J Clin Pharmacol Ther*. 2007;45(12):623-30.

Kalesnykiene V, Sorri I, Voutilainen R, Uusitupa M, Niskanen L, Uusitalo H. The effect of glycaemic control on the quantitative characteristics of retinopathy lesions in patients with type 2 diabetes mellitus: 10-year follow-up study. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(3):335-41.

Kasai T, Miyauchi K, Kajimoto K, Kubota N, Kurata T, Daida H. Influence of diabetes on >10-year outcomes after percutaneous coronary intervention. *Heart Vessels*. 2008;23(3):149-54.

Kawamori R, Fujita T, Matsuoka H, Umemura S, Saito Y. Relation between cardiovascular complications and blood pressure/blood glucose control in diabetic patients with hypertension receiving long-term candesartan cilexetil therapy: Challenge-DM study. *Diabetes Res Clin Pract*. 2009;83(2):241-8.

Kengne AP, Patel A, Colagiuri S, Heller S, Hamet P, Marre M, et al. The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study. *Diabetologia*. 2010;53(5):821-31.

Kim C, Edelstein SL, Crandall JP, Dabelea D, Kitabchi AE, Hamman RF, et al. Menopause and risk of diabetes in the Diabetes Prevention Program. *Menopause.* 2011;18(8):857-68.

Kolb H, Martin S, Lodwig V, Heinemann L, Scherbaum WA, Schneider B. Are type 2 diabetes patients who self-monitor blood glucose special? The role of confounders in the observational ROSSO study. *J Diabetes Sci Technol*. 2009;3(6):1507-15.

Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. *Clin Ther*. 2009;31(11):2608-17.

Krum H, McMurray JJV, Horton E, Gerlock T, Holzhauer B, Zuurman L, et al. Baseline characteristics of the Nateglinide and Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial population: comparison with other diabetes prevention trials. *Cardiovasc Ther*. 2010;28(2):124-32.

Kunte H, Schmidt S, Eliasziw M, del Zoppo GJ, Simard JM, Masuhr F, et al. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. *Stroke.* 2007;38(9):2526-30.

Lee LJ, Fahrbach JL, Nelson LM, McLeod LD, Martin SA, Sun P, et al. Effects of insulin initiation on patient-reported outcomes in patients with type 2 diabetes: results from the durable trial. *Diabetes Res Clin Pract*. 2010;89(2):157-66.

Lee VWY, Ho ICH, Chan WSY, Tam KY, Lee KKC. Statin utilization patterns for the primary prevention of cardiovascular events: a retrospective study in patients with diabetes mellitus in Hong Kong. *Am J Cardiovasc Drugs*. 2008;8(3):199-205.

Li D, Yeung S-CJ, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009;137(2):482-8.

Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. *Diabetes Obes Metab*. 2009;11(12):1138-44.

Mather KJ, Funahashi T, Matsuzawa Y, Edelstein S, Bray GA, Kahn SE, et al. Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. *Diabetes.* 2008;57(4):980-6.

McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Saf*. 2007;16(7):711-25.

McBride PE, Einerson JA, Grant H, Sargent C, Underbakke G, Vitcenda M, et al. Putting the Diabetes Prevention Program into practice: a program for weight loss and cardiovascular risk reduction for patients with metabolic syndrome or type 2 diabetes mellitus. *J Nutr Health Aging*. 2008;12(10):745S-9S.

Paddison CAM, Eborall HC, Sutton S, French DP, Vasconcelos J, Prevost AT, et al. Are people with negative diabetes screening tests falsely reassured? Parallel group cohort study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ*. 2009;339:b4535.

Pendergrass M, Fenton C, Haffner SM, Chen W. Exenatide and sitagliptin are not associated with increased risk of acute renal failure: a retrospective claims analysis. *Diabetes Obes Metab*. 2012;14(7):596-600.

Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. *Clin Ther*. 2011;33(11):1781-91.

Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. *BMC med*. 2007;5:17.

Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care*. 2008;31(8):1672-8.

Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2009(1).

Saaristo T, Barengo N, Korpi-Hyovalti E, Oksa H, Puolijoki H, Saltevo J, et al. High prevalence of obesity, central obesity and abnormal glucose tolerance in the middle-aged Finnish population. *BMC Public Health*. 2008;8(1):423.

Sadikot SM, Mogensen CE. Risk of coronary artery disease associated with initial sulphonylurea treatment of patients with type 2 diabetes: a matched case-control study. *Diabetes Res Clin Pract*. 2008;82(3):391-5.

Schneider B, Martin S, Heinemann L, Lodwig V, Kolb H. Interrelations between diabetes therapy, self-monitoring of blood glucose, blood glucose and non-fatal or fatal endpoints in patients with type 2 diabetes / results of a longitudinal cohort study (ROSSO 5). *Arzneimittelforschung*. 2007;57(12):762-9.

Schweizer A, Dejager S, Foley JE, Couturier A, Ligueros-Saylan M, Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population.[Erratum appears in *Diabetes Obes Metab*. 2010 Sep;12(9):832]. *Diabetes Obes Metab*. 2010;12(6):485-94.

Stevens L. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2005(3).

Sullivan SD, Garrison LP, Jr., Rinde H, Kolberg J, Moler EJ. Cost-effectiveness of risk stratification for preventing type 2 diabetes using a multi-marker diabetes risk score. *J Med Econ*. 2011;14(5):609-16.

Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes.[Erratum appears in *Diabetologia*. 2009 Nov;52(1):2470 Note: Control Group [added]]. *Diabetologia*. 2009;52(11):2288-98.

Walsh M, Spurling G. Aspirin in type 2 diabetes: is there any evidence base? *BMJ*. 2008;337:a1902.

Wilding JPH, Hardy K. Glucagon-like peptide-1 analogues for type 2 diabetes. *BMJ*. 2011;342:d410.

Yeboah J, Bertoni AG, Herrington DM, Post WS, Burke GL. Impaired fasting glucose

and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2011;58(2):140-6.

Zhang C-Y, Sun A-J, Zhang S-N, Wu C-n, Fu M-Q, Xia G, et al. Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis. *Ann Med*. 2010;42(4):305-15.

Zhuo X, Zhang P, Gregg EW, Barker L, Hoerger TJ, Pearson-Clarke T, et al. A Nationwide Community-Based Lifestyle Program Could Delay Or Prevent Type 2 Diabetes Cases And Save $5.7 Billion In 25 Years. *Health Aff (Millwood)*. 2012;31(1):50-60.

Wrong publication type

Bloomgarden ZT. Glycemic Control in Diabetes: A Tale of Three Studies. *Diabetes Care*. 2008;31(9):1913-9.

Boehm CM, Smith S. Altering the course. Screening for prediabetes. *Adv Nurse Pract*. 2007;15(11):43-6.

Caballero AE. Long-term benefits of insulin therapy and glycemic control in overweight and obese adults with type 2 diabetes. *J Diabetes Complications*. 2009;23(2):143-52.

Dailey G. Overall mortality in diabetes mellitus: where do we stand today? *Diabetes Technol Ther*. 2011;13 Suppl 1:S65-74.

Delahanty LM, Nathan DM. Implications of the diabetes prevention program and Look AHEAD clinical trials for lifestyle interventions. *J Am Diet Assoc*. 2008;108(4 Suppl 1):S66-72.

Demssie YN, Soran H, Younis N. Tight glycaemic control and cardiovascular disease in type 2 diabetes. *Br J Hosp Med.* 2009;70(1):31-2, 4.

Diabetes UK. Early Identification of people with and at high risk of type 2 diabetes and interventions for those at high risk. 2012 [cited 2012 November 30,]; Available from: http://www.diabetes.org.uk/Documents/Position%20statements/Early%20identification%20of%20Type%202%20diabetes%20Position%20statement.pdf.

Dominguez LJ, Paolisso G, Barbagallo M. Glucose control in the older patient: from intensive, to effective and safe. *Aging Clin Exp Res*. 2010;22(4):274-80.

Donnelly R. Effect of pioglitazone on the drivers of cardiovascular risk in type 2 diabetes. *Int J Clin Pract*. 2007;61(7):1160-9.

Dunn FL. Management of dyslipidemia in people with type 2 diabetes mellitus. *Rev Endocr Metab Disord*. 2010;11(1):41-51.

Edwards SP. Prevention: Nipped in the bud. *Nature*. 2012;485(7398):S18-9.

Finucane TE. "Tight control" in geriatrics: the emperor wears a thong. *J Am Geriatr Soc*. 2012;60(8):1571-5.

Fradkin JE, Roberts BT, Rodgers GP. What's preventing us from preventing type 2 diabetes? *N Engl J Med*. 2012;367(13):1177-9.

Fravel MA, McDanel DL, Ross MB, Moores KG, Starry MJ. Special considerations for treatment of type 2 diabetes mellitus in the elderly. *Am J Health Syst Pharm*. 2011;68(6):500-9.

Gebel E. Stopping diabetes before it starts: diabetes prevention works out at the Y. *Diabetes Forecast*. 2012;65(2):44-6.

Ghiadoni L. Management of high blood pressure in type 2 diabetes: perindopril/indapamide fixed-dose combination and the ADVANCE trial [corrected].[Erratum appears in *Expert Opin Pharmacother*. 2010 Aug;11(11);1963]. *Expert Opin Pharmacother*. 2010;11(10):1647-57.

Goldberg RB, Holman R, Drucker DJ. Clinical decisions. Management of type 2 diabetes.[Erratum appears in *N Engl J Med*. 2008 May 1;358(18):1977]. *N Engl J Med*. 2008;358(3):293-7.

Gomez-Huelgas R, Bernal-Lopez MR, Mancera J, Tinahones FJ. HbA1c for diabetes diagnosis. Are we ready? *Diabet Med*. 2010;27(3):367-8.

Grzywa M, Mazur A, Skrzypiec J. Screening for the detection of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes in welfare homes residents from south-eastern region of Poland. *Int J Clin Pract*. 2011;65(7):818-9.

Hawkes N. Screening for type 2 diabetes doesn't affect mortality at 10 years. *BMJ*. 2012;345:e6687.

Idris I. Safety of very tight glucose control in type 2 diabetes in question. *Diabetes Obes Metab*. 2008;10(5):438.

Kalaitzidis RG, Bakris GL. Pros and cons of aggressive blood pressure lowering in patients with type 2 diabetes. *Curr Vasc Pharmacol*. 2012;10(2):156-61.

Kamp SJ. Diabetes in older adults. Consider presentation, functioning and more. *Adv Nurse Pract*. 2007;15(11):37-8, 40-2.

Karthikeyan VJ, Bakris G, MacFadyen RJ. The ADVANCE trial: further PROGRESS with HOPE. *J Hum Hypertens*. 2007;21(12):911-3.

Katula JA, Vitolins MZ, Rosenberger EL, Blackwell C, Espeland MA, Lawlor MS, et al. Healthy Living Partnerships to Prevent Diabetes (HELP PD): design and methods. *Contemp Clin Trials*. 2010;31(1):71-81.

Khunti K, Davies M. Should we screen for type 2 diabetes: Yes. *BMJ*. 2012;345:e4514.

Klein Woolthuis EP, de Grauw WJC, van Weel C. Opportunistic screening for type 2 diabetes in primary care. *Lancet*. 2010;376(9742):683-4.

Lindstrom J, Absetz P, Hemio K, Peltomaki P, Peltonen M. Reducing the risk of type 2 diabetes with nutrition and physical activity - efficacy and implementation of lifestyle interventions in Finland. *Public Health Nutr*. 2010;13(6A):993-9.

Lloret-Linares C, Greenfield JR, Czernichow S. Effect of weight-reducing agents on glycaemic parameters and progression to Type 2 diabetes: a review. *Diabet Med*. 2008;25(10):1142-50.

Ma J, King AC, Wilson SR, Xiao L, Stafford RS. Evaluation of lifestyle interventions to treat elevated cardiometabolic risk in primary care (E-LITE): a randomized controlled trial. *BMC Fam Pract*. 2009;10:71.

Meier M, Hummel M. Cardiovascular disease and intensive glucose control in type 2 diabetes mellitus: moving practice toward

evidence-based strategies. *Vasc Health Risk Manag*. 2009;5:859-71.

Neumiller JJ, Setter SM. Review of linagliptin for the treatment of type 2 diabetes mellitus. *Clin Ther*. 2012;34(5):993-1005.

Reboldi G, Gentile G, Angeli F, Verdecchia P. Optimal therapy in hypertensive subjects with diabetes mellitus. *Curr Atheroscler Rep*. 2011;13(2):176-85.

Rutten G. Screening for type 2 diabetes--where are we now? *Lancet*. 2010;375(9723):1324-6.

Scott T. Does pioglitazone benefit patients with type 2 diabetes? *Am Fam Physician*. 2007;76(7):969-70.

Seley JJ. Does tight glycemic control increase the risk of death? *Am J Nurs*. 2008;108(11):31.

Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EAM, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association.[Erratum appears in Diabetes Care. 2009 Apr;32(4):754]. *Diabetes Care*. 2009;32(1):187-92.

Soejima H, Morimoto T, Saito Y, Ogawa H. Aspirin for the primary prevention of cardiovascular events in patients with peripheral artery disease or diabetes mellitus. Analyses from the JPAD, POPADAD and AAA trials. *Thromb Haemost*. 2010;104(6):1085-8.

Younis N, Soran H, Hassanein M. Cardiovascular disease and intensive glucose lowering in type 2 diabetes. *QJM*. 2009;102(4):293-6.

Wrong population due to advanced diabetes (A1c >8) or long duration (>1 year)

Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care*. 2011;34(6):1318-9.

Akin I, Bufe A, Eckardt L, Reinecke H, Senges J, Richardt G, et al. Comparison of outcomes in patients with insulin-dependent versus non-insulin dependent diabetes mellitus receiving drug-eluting stents (from the first phase of the prospective multicenter German DES.DE registry). *Am J Cardiol*. 2010;106(9):1201-7.

Ali MK, Feeney P, Hire D, Simmons DL, O'Connor PJ, Ganz-Lord F, et al. Glycaemia and correlates of patient-reported outcomes in ACCORD trial participants. *Diabet Med*. 2012;29(7):e67-74.

Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jorgensen CH, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. *Diabetologia*. 2010;53(12):2546-53.

Aschner P, Chan J, Owens DR, Picard S, Wang E, Dain M-P, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. *Lancet*. 2012;379(9833):2262-9.

Athyros VG, Hatzitolios A, Karagiannis A, Didangelos TP, Iliadis F, Dolgyras S, et al. Initiative for a new diabetes therapeutic approach in a Mediterranean country: the INDEED study. *Curr Med Res Opin*. 2009;25(8):1931-40.

Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC med*. 2013;11(43).

Balducci S, Zanuso S, Massarini M, Corigliano G, Nicolucci A, Missori S, et al. The Italian Diabetes and Exercise Study (IDES): design and methods for a prospective Italian multicentre trial of intensive lifestyle intervention in people with type 2 diabetes and the metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2008;18(9):585-95.

Bebakar WMW, Chow CC, Kadir KA, Suwanwalaikorn S, Vaz JA, Bech OM, et al. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9(5):724-32.

Bergenstal RM, Li Y, Porter TKB, Weaver C, Han J. Exenatide once weekly improved glycaemic control, cardiometabolic risk factors and a composite index of an HbA1c < 7%, without weight gain or hypoglycaemia, over 52 weeks. *Diabetes Obes Metab*. 2013;15(3):264-71.

Best JH, Hoogwerf BJ, Herman WH, Pelletier EM, Smith DB, Wenten M, et al. Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. *Diabetes Care*. 2011;34(1):90-5.

Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (Minneap)*. 2013;41(2):72-84.

Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. *Cancer Epidemiol Biomarkers Prev*. 2012;21(2):280-6.

Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care*. 2010;33(6):1304-8.

Brooks MM, Chaitman BR, Nesto RW, Hardison RM, Feit F, Gersh BJ, et al. Clinical and angiographic risk stratification and differential impact on treatment outcomes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Circulation*. 2012;126(17):2115-24.

Caterson ID, Finer N, Coutinho W, Van Gaal LF, Maggioni AP, Torp-Pedersen C, et al. Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab*. 2012;14(6):523-30.

Chalmers J, Joshi R, Kengne AP, MacMahon S. Blood pressure lowering with fixed combination perindopril-indapamide: key findings from ADVANCE. *J Hypertens*. 2008;Supplement : official journal of the

International Society of Hypertension. 26(2):S11-5.

Chan JC, So W-Y, Yeung C-Y, Ko GT, Lau I-T, Tsang M-W, et al. Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care*. 2009;32(6):977-82.

Chang C-H, Lin J-W, Wu L-C, Lai M-S, Chuang L-M. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2012;97(7):E1170-5.

Cook W, Bryzinski B, Slater J, Frederich R, Allen E. Saxagliptin efficacy and safety in patients with type 2 diabetes mellitus and cardiovascular disease history or cardiovascular risk factors: results of a pooled analysis of phase 3 clinical trials. *Postgrad Med*. 2013;125(3):145-54.

Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;52(9):1766-77.

Curtis PJ, Sampson M, Potter J, Dhatariya K, Kroon PA, Cassidy A. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: a 1-year, double-blind, randomized, controlled trial. *Diabetes Care*. 2012;35(2):226-32.

Davidson JA, McMorn SO, Waterhouse BR, Cobitz AR. A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and tolerability of combination therapy with rosiglitazone and sulfonylurea in African American and Hispanic American patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy. *Clin Ther*. 2007;29(9):1900-14.

Davies M, Lavalle-Gonzalez F, Storms F, Gomis R, Group ALS. Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the AT.LANTUS trial. *Diabetes Obes Metab*. 2008;10(5):387-99.

Dobs AS, Goldstein BJ, Aschner P, Horton ES, Umpierrez GE, Duran L, et al. Efficacy and safety of sitagliptin added to ongoing metformin and rosiglitazone combination therapy in a randomized placebo-controlled 54-week trial in patients with type 2 diabetes. Journal of diabetes. 2013;5(1):68-79.

Donadon V, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int.* 2010;30(5):750-8.

Donadon V, Balbi M, Valent F, Avogaro A. Glycated hemoglobin and antidiabetic strategies as risk factors for hepatocellular carcinoma. *World J Gastroenterol*. 2010;16(24):3025-32.

Dormandy J, Bhattacharya M, van Troostenburg de Bruyn A-R, investigators PR. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Saf*. 2009;32(3):187-202.

Erdmann E, Spanheimer R, Charbonnel B, Investigators PRS. Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the

PROactive study (PROactive 20). Journal Of Diabetes. 2010;2(3):212-20.

Evans JMM, Doney ASF, AlZadjali MA, Ogston SA, Petrie JR, Morris AD, et al. Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. *Am J Cardiol*. 2010;106(7):1006-10.

Fal AM, Jankowska B, Uchmanowicz I, Sen M, Panaszek B, Polanski J. Type 2 diabetes quality of life patients treated with insulin and oral hypoglycemic medication. *Acta Diabetol*. 2011;48(3):237-42.

Faludi P, Brodows R, Burger J, Ivanyi T, Braun DK. The effect of exenatide re-exposure on safety and efficacy. *Peptides*. 2009;30(9):1771-4.

Farkouh ME, Aneja A, Reeder GS, Smars PA, Lennon RJ, Wiste HJ, et al. Usefulness of diabetes mellitus to predict long-term outcomes in patients with unstable angina pectoris. *Am J Cardiol*. 2009;104(4):492-7.

Fegan PG, Davis WA, Kamber N, Sivakumar S, Beilby J, Davis TME. Renin-angiotensin-aldosterone system blockade and urinary albumin excretion in community-based patients with Type 2 diabetes: the Fremantle Diabetes Study. *Diabet Med*. 2011;28(7):849-55.

Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahren B, Byiers S, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy.[Erratum appears in *Diabetes Obes Metab*. 2009 Apr;11(4):405]. *Diabetes Obes Metab*. 2009;11(2):157-66.

Filion KB, Joseph L, Boivin J-F, Suissa S, Brophy JM. Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2011;20(8):785-96.

Fonseca VA, Ferrannini E, Wilding JP, Wilpshaar W, Dhanjal P, Ball G, et al. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. *J Diabetes Complications*. 2013;27(3):268-73.

Giles TD, Elkayam U, Bhattacharya M, Perez A, Miller AB. Comparison of pioglitazone vs glyburide in early heart failure: insights from a randomized controlled study of patients with type 2 diabetes and mild cardiac disease. *Congest Heart Fail*. 2010;16(3):111-7.

Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail*. 2008;14(6):445-52.

Goke B, Hershon K, Kerr D, Calle Pascual A, Schweizer A, Foley J, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naive patients with type 2 diabetes: comparison with metformin. *Horm Metab Res*. 2008;40(12):892-5.

Gonzalez-Clemente JM, Pinies JA, Calle-Pascual A, Saavedra A, Sanchez C, Bellido D, et al. Cardiovascular risk factor management is poorer in diabetic patients with undiagnosed peripheral arterial disease than in those with known coronary heart disease or cerebrovascular disease. Results of a nationwide study in tertiary diabetes centres. *Diabet Med*. 2008;25(4):427-34.

Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, Williams LK. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2010;95(2):592-600.

Haller H, Ito S, Izzo JL, Jr., Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011;364(10):907-17.

Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia*. 2009;52(12):2499-506.

Hsu C-C, Wahlqvist ML, Lee M-S, Tsai H-N. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis*. 2011;24(3):485-93.

Jermendy G, Hungarian RG, Erdesz D, Nagy L, Yin D, Phatak H, et al. Outcomes of adding second hypoglycemic drug after metformin monotherapy failure among type 2 diabetes in Hungary. *Health Qual Life Outcomes*. 2008;6:88.

Kadoglou NPE, Iliadis F, Liapis CD, Perrea D, Angelopoulou N, Alevizos M. Beneficial effects of combined treatment with rosiglitazone and exercise on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care*. 2007;30(9):2242-4.

Kaku K, Daida H, Kashiwagi A, Yamashina A, Yamazaki T, Momomura S-i, et al. Long-term effects of pioglitazone in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. *Curr Med Res Opin*. 2009;25(12):2925-32.

Kapitza C, Heise T, Birman P, Jallet K, Ramis J, Balena R. Pharmacokinetic and pharmacodynamic properties of taspoglutide, a once-weekly, human GLP-1 analogue, after single-dose administration in patients with Type 2 diabetes. *Diabet Med*. 2009;26(11):1156-64.

Khanna A, Bush AL, Swint JM, Peskin MF, Street RL, Jr., Naik AD. Hemoglobin A1c improvements and better diabetes-specific quality of life among participants completing diabetes self-management programs: a nested cohort study. *Health Qual Life Outcomes*. 2012;10:48.

Kikuchi M, Kaku K, Odawara M, Momomura S-i, Ishii R. Efficacy and tolerability of rosiglitazone and pioglitazone in drug-naive Japanese patients with type 2 diabetes mellitus: a double-blind, 28 weeks' treatment, comparative study. *Curr Med Res Opin*. 2012;28(6):1007-16.

Kleefstra N, Hortensius J, Logtenberg SJJ, Slingerland RJ, Groenier KH, Houweling ST, et al. Self-monitoring of blood glucose in tablet-treated type 2 diabetic patients (ZODIAC). *Neth J Med*. 2010;68(1):311-6.

Kooy A, de Jager J, Lehert P, Bets D, Wulffele MG, Donker AJM, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;169(6):616-25.

Kostev K, Dippel FW, Rockel T, Siegmund T. Risk of diabetic foot ulceration during treatment with insulin glargine and NPH insulin. *J Wound Care*. 2012;21(10):483-4, 6-9.

Kress S, Kostev K, Dippel FW, Giani G, Rathmann W. Micro- and macrovascular

outcomes in Type 2 diabetic patients treated with insulin glulisine or human regular insulin: a retrospective database analysis. *Int J Clin Pharmacol Ther*. 2012;50(11):821-9.

Lewis JD, Capra AM, Achacoso NS, Ferrara A, Levin TR, Quesenberry CP, Jr., et al. Thiazolidinedione therapy is not associated with increased colonic neoplasia risk in patients with diabetes mellitus. *Gastroenterology*. 2008;135(6):1914-23, 23.e1.

Li C, Xia J, Zhang G, Wang S, Wang L. Nateglinide versus repaglinide for type 2 diabetes mellitus in China. *Acta Diabetol*. 2009;46(4):325-33.

Look ARG, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-54.

Lowe JM, Mensch M, McElduff P, Fitzgerald M, Attia J. Does an advanced insulin education programme improve outcomes and health service use for people with Type 2 diabetes? A 5-year follow-up of the Newcastle Empowerment course. *Diabet Med*. 2009;26(12):1277-81.

Luk AO, Yang X, Ma RC, Ng VW, Yu LW, Lau WW, et al. Association of statin use and development of renal dysfunction in type 2 diabetes--the Hong Kong Diabetes Registry. *Diabetes Res Clin Pract*. 2010;88(3):227-33.

Lukashevich V, Schweizer A, Shao Q, Groop PH, Kothny W. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. *Diabetes Obes Metab*. 2011;13(10):947-54.

MacDonald MR, Eurich DT, Majumdar SR, Lewsey JD, Bhagra S, Jhund PS, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care*. 2010;33(6):1213-8.

Maddigan SL, Majumdar SR, Toth EL, Feeny DH, Johnson JA, Investigators D. Health-related quality of life deficits associated with varying degrees of disease severity in type 2 diabetes. *Health Qual Life Outcomes*. 2003;1:78.

Makino H, Haneda M, Babazono T, Moriya T, Ito S, Iwamoto Y, et al. Microalbuminuria reduction with telmisartan in normotensive and hypertensive Japanese patients with type 2 diabetes: a post-hoc analysis of The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study. *Hypertens Res*. 2008;31(4):657-64.

Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, Vescovi PP, et al. Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone. 2009;45(4):784-8.

Masuda H, Sakamoto M, Irie J, Kitaoka A, Shiono K, Inoue G, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naive type 2 diabetic patients. *Diabetes Obes Metab*. 2008;10(12):1261-5.

Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch Intern Med*. 2008;168(8):820-5.

Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L, Investigators D. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J*. 2008;29(2):166-76.

Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L, Investigators D. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. *Diabetologia*. 2011;54(6):1308-17.

Mellbin LG, Malmberg K, Waldenstrom A, Wedel H, Ryden L, investigators D. Prognostic implications of hypoglycaemic episodes during hospitalisation for myocardial infarction in patients with type 2 diabetes: a report from the DIGAMI 2 trial. *Heart.* 2009;95(9):721-7.

Miao Y, Dobre D, Heerspink HJL, Brenner BM, Cooper ME, Parving HH, et al. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial.[Erratum appears in *Diabetologia*. 2011 Aug;54(8):2209]. *Diabetologia*. 2011;54(1):44-50.

Miao Y, Ottenbros SA, Laverman GD, Brenner BM, Cooper ME, Parving H-H, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. *Hypertension*. 2011;58(1):2-7.

Miksch A, Laux G, Ose D, Joos S, Campbell S, Riens B, et al. Is there a survival benefit within a German primary care-based disease management program? *Am J Manag Care*. 2010;16(1):49-54.

Milman U, Blum S, Shapira C, Aronson D, Miller-Lotan R, Anbinder Y, et al. Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 genotype: a prospective double-blinded clinical trial. *Arterioscler Thromb Vasc Biol*. 2008;28(2):341-7.

Mohan V, Yang W, Son H-Y, Xu L, Noble L, Langdon RB, et al. Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India, and Korea. *Diabetes Res Clin Pract*. 2009;83(1):106-16.

Mohanram A, Zhang Z, Shahinfar S, Lyle PA, Toto RD. The effect of losartan on hemoglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes. *Kidney Int*. 2008;73(5):630-6.

Monami M, Balzi D, Lamanna C, Barchielli A, Masotti G, Buiatti E, et al. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. *Diabetes Metab Res Rev*. 2007;23(6):479-84.

Monami M, Colombi C, Balzi D, Dicembrini I, Giannini S, Melani C, et al. Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. *Diabetes Care*. 2011;34(1):129-31.

Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. *Diabetes Care*. 2008;31(2):199-203.

Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E. Sulphonylureas and cancer: a case-control study. *Acta Diabetol*. 2009;46(4):279-84.

Monami M, Lamanna C, Pala L, Bardini G, Cresci B, Francesconi P, et al. Treatment with insulin secretagogues and cancer-related mortality in type 2 diabetic patients a retrospective cohort study. *Exp Clin Endocrinol Diabetes*. 2008;116(3):184-9.

Monami M, Marchionni N, Mannucci E. Winners and losers at the rosiglitazone gamble A meta-analytical approach at the definition of the cardiovascular risk profile of rosiglitazone. *Diabetes Res Clin Pract*. 2008;82(1):48-57.

Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia*. 2012;55(7):1953-62.

Newman CB, Szarek M, Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, et al. The safety and tolerability of atorvastatin 10 mg in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diab Vasc Dis Res*. 2008;5(3):177-83.

Nicolucci A, Balducci S, Cardelli P, Cavallo S, Fallucca S, Bazuro A, et al. Relationship of exercise volume to improvements of quality of life with supervised exercise training in patients with type 2 diabetes in a randomised controlled trial: the Italian Diabetes and Exercise Study (IDES). *Diabetologia*. 2012;55(3):579-88.

Ninomiya T, Zoungas S, Neal B, Woodward M, Patel A, Perkovic V, et al. Efficacy and safety of routine blood pressure lowering in older patients with diabetes: results from the ADVANCE trial. *J Hypertens*. 2010;28(6):1141-9.

Opsteen C, Qi Y, Zinman B, Retnakaran R. Effect of short-term intensive insulin therapy on quality of life in type 2 diabetes. *J Eval Clin Pract*. 2012;18(2):256-61.

Origin Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-28.

Oyer DS, Shepherd MD, Coulter FC, Bhargava A, Brett J, Chu P-L, et al. A(1c) control in a primary care setting: self-titrating an insulin analog pre-mix (INITIATEplus trial). *Am J Med*. 2009;122(11):1043-9.

Oyer DS, Shepherd MD, Coulter FC, Bhargava A, Deluzio AJ, Chu P-L, et al. Efficacy and tolerability of self-titrated biphasic insulin aspart 70/30 in patients aged >65 years with type 2 diabetes: an exploratory post hoc subanalysis of the INITIATEplus trial. *Clin Ther*. 2011;33(7):874-83.

Paile-Hyvarinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: a double-blind randomised placebo controlled 6-month trial. *BMC Fam Pract*. 2007;8:34.

Pala L, Monami M, Lamanna C, Cresci B, Colombi C, Bardini G, et al. Failure to metformin and insulin secretagogue monotherapy: an observational cohort study. *Acta Diabetol*. 2010;47(Suppl 1):7-11.

Pan CY, Yang W, Tou C, Gause-Nilsson I, Zhao J. Efficacy and safety of saxagliptin in drug-naive Asian patients with type 2

diabetes mellitus: a randomized controlled trial. *Diabetes Metab Res Rev*. 2012;28(3):268-75.

Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care*. 2010;33(6):1224-9.

Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Nutter B, et al. The risk of overall mortality in patients with Type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. *Diabet Med*. 2012;29(8):1029-35.

Parving H-H, Brenner BM, McMurray JJV, de Zeeuw D, Haffner SM, Solomon SD, et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant*. 2009;24(5):1663-71.

Parving H-H, Brenner BM, McMurray JJV, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-13.

Parving H-H, Persson F, Lewis JB, Lewis EJ, Hollenberg NK, Investigators AS. Aliskiren combined with losartan in type 2 diabetes and nephropathy.[Reprint in Ugeskr Laeger. 2009 Mar 9;171(11):881-4; PMID: 19291865]. *N Engl J Med*. 2008;358(23):2433-46.

Pattzi HMR, Pitale S, Alpizar M, Bennett C, O'Farrell AM, Li J, et al. Dutogliptin, a selective DPP4 inhibitor, improves glycaemic control in patients with type 2 diabetes: a 12-week, double-blind, randomized, placebo-controlled, multicentre trial. *Diabetes Obes Metab*. 2010;12(4):348-55.

Pfutzner A, Paz-Pacheco E, Allen E, Frederich R, Chen R, Investigators CV. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. *Diabetes Obes Metab*. 2011;13(6):567-76.

Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q, Alogliptin Study G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. *Diabetes Obes Metab*. 2009;11(2):167-76.

Pratley RE, Reusch JEB, Fleck PR, Wilson CA, Mekki Q, Alogliptin Study G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Curr Med Res Opin*. 2009;25(10):2361-71.

Rajamani K, Colman PG, Li LP, Best JD, Voysey M, D'Emden MC, et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet*. 2009;373(9677):1780-8.

Raz I, Fonseca V, Kipnes M, Durrwell L, Hoekstra J, Boldrin M, et al. Efficacy and safety of taspoglutide monotherapy in drug-naive type 2 diabetic patients after 24 weeks of treatment: results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1). *Diabetes Care*. 2012;35(3):485-7.

Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, et al.

Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care*. 2010;33(5):983-90.

Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R, et al. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. *Curr Med Res Opin*. 2009;25(10):2401-11.

Shibayama T, Kobayashi K, Takano A, Kadowaki T, Kazuma K. Effectiveness of lifestyle counseling by certified expert nurse of Japan for non-insulin-treated diabetic outpatients: a 1-year randomized controlled trial. *Diabetes Res Clin Pract*. 2007;76(2):265-8.

Sone H, Tanaka S, Iimuro S, Oida K, Yamasaki Y, Oikawa S, et al. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). *Diabetologia*. 2010;53(3):419-28.

Trento M, Basile M, Borgo E, Grassi G, Scuntero P, Trinetta A, et al. A randomised controlled clinical trial of nurse-, dietitian- and pedagogist-led Group Care for the management of Type 2 diabetes. *J Endocrinol Invest*. 2008;31(11):1038-42.

Trento M, Gamba S, Gentile L, Grassi G, Miselli V, Morone G, et al. Rethink Organization to iMprove Education and Outcomes (ROMEO): a multicenter randomized trial of lifestyle intervention by group care to manage type 2 diabetes. *Diabetes Care*. 2010;33(4):745-7.

Tseng C-H. Insulin use is not significantly predictive for prostate cancer mortality in diabetic patients: a 12-year follow-up study. *BJU Int*. 2012;110(5):668-73.

Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K, et al. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. *Arch Intern Med*. 2009;169(2):163-71.

Woodward A, Wallymahmed M, Wilding JP, Gill GV. Nurse-led clinics for strict hypertension control are effective long term: a 7 year follow-up study. *Diabet Med*. 2010;27(8):933-7.

In systematic review, not directly used

Asche CV, McAdam-Marx C, Shane-McWhorter L, Sheng X, Plauschinat CA. Association between oral antidiabetic use, adverse events and outcomes in patients with type 2 diabetes. *Diabetes Obes Metab*. 2008;10(8):638-45.

Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(8):716-21.

Azoulay L, Schneider-Lindner V, Dell'aniello S, Filion KB, Suissa S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(4):343-50.

Azoulay L, Schneider-Lindner V, Dell'aniello S, Schiffrin A, Suissa S. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(4):335-42.

Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, Pollak MN, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ*. 2012;344:e3645.

Bazelier MT, Gallagher AM, van Staa T-P, Cooper C, Leufkens HGM, Vestergaard P, et al. Use of thiazolidinediones and risk of osteoporotic fracture: disease or drugs? *Pharmacoepidemiol Drug Saf*. 2012;21(5):507-14.

Berthet S, Olivier P, Montastruc J-L, Lapeyre-Mestre M. Drug safety of rosiglitazone and pioglitazone in France: a study using the French PharmacoVigilance database. *BMC Clin Pharml*. 2011;11:5.

Bilik D, McEwen LN, Brown MB, Pomeroy NE, Kim C, Asao K, et al. Thiazolidinediones and fractures: evidence from translating research into action for diabetes. *J Clin Endocrinol Metab*. 2010;95(10):4560-5.

Bo S, Ciccone G, Rosato R, Villois P, Appendino G, Ghigo E, et al. Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients. *Diabetes Obes Metab*. 2012;14(1):23-9.

Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.

Chang C-H, Lin J-W, Wu L-C, Lai M-S, Chuang L-M, Chan KA. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology*. 2012;55(5):1462-72.

Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. *Arch Intern Med*. 2009;169(15):1395-402.

Dormuth CR, Maclure M, Carney G, Schneeweiss S, Bassett K, Wright JM. Rosiglitazone and myocardial infarction in patients previously prescribed metformin.[Erratum appears in *PLoS ONE*. 2010;5(7). doi: 10.1371/annotation/3330720e-5520-4211-91f3-d3b3d20e9804]. *PLoS ONE* [Electronic Resource]. 2009;4(6):e6080.

Ferrara A, Lewis JD, Quesenberry CP, Jr., Peng T, Strom BL, Van Den Eeden SK, et al. Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care*. 2011;34(4):923-9.

Fong DS, Contreras R. Glitazone use associated with diabetic macular edema. *Am J Ophthalmol*. 2009;147(4):583-6.e1.

Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010;304(4):411-8.

Horsdal HT, Sondergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. *Pharmacoepidemiol Drug Saf*. 2011;20(4):331-7.

Hsiao F-Y, Huang W-F, Wen Y-W, Chen P-F, Kuo KN, Tsai Y-W. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf. 2009;32(8):675-90.

Hsieh M-C, Lee T-C, Cheng S-M, Tu S-T, Yen M-H, Tseng C-H. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res*. 2012;2012:413782.

Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med*. 2012;172(13):1005-11.

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial.[Erratum appears in *Lancet*. 2010 Oct 30;376(9751):1466]. *Lancet*. 2010;376(9739):419-30.

Koro CE, Fu Q, Stender M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. *Pharmacoepidemiol Drug Saf*. 2008;17(10):989-96.

Koro CE, Sowell MO, Stender M, Qizilbash N. The risk of myopathy associated with thiazolidinediones and statins in patients with type 2 diabetes: a nested case-control analysis. *Clin Ther*. 2008;30(3):535-42.

Landman GWD, Kleefstra N, van Hateren KJJ, Groenier KH, Gans ROB, Bilo HJG. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care*. 2010;33(2):322-6.

Lee M-S, Hsu C-C, Wahlqvist ML, Tsai H-N, Chang Y-H, Huang Y-C. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer*. 2011;11:20.

Lehman DM, Lorenzo C, Hernandez J, Wang C-P. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. *Diabetes Care*. 2012;35(5):1002-7.

Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP, Jr., et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care*. 2011;34(4):916-22.

Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JMM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care*. 2009;32(9):1620-5.

Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. *J Natl Cancer Inst*. 2012;104(18):1411-21.

McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. *Eur J Heart Fail*. 2008;10(7):703-8.

Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study.[Erratum appears in *Eur Heart J*. 2012 May;33(10):1183]. *Eur Heart J*. 2011;32(15):1900-8.

Stockl KM, Le L, Zhang S, Harada ASM. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. *Pharmacoepidemiol Drug Saf*. 2009;18(2):166-74.

Tseng C-H. Diabetes, insulin use, and non-Hodgkin lymphoma mortality in Taiwan. *Metabolism.* 2012;61(7):1003-9.

Wrong comparison

Alssema M, Vistisen D, Heymans MW, Nijpels G, Glumer C, Zimmet PZ, et al. The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) update of the Finnish diabetes risk score for prediction of incident type 2 diabetes. *Diabetologia*. 2011;54(5):1004-12.

Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, et al. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. *Diabetologia*. 2012;55(3):644-53.

Boyko EJ, Gerstein HC, Mohan V, Yusuf S, Sheridan P, Anand S, et al. Effects of ethnicity on diabetes incidence and prevention: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabet Med*. 2010;27(11):1226-32.

Burke TA, Sturkenboom MC, Ohman-Strickland PA, Wentworth CE, Rhoads GG. The effect of antihypertensive drugs and drug combinations on the incidence of new-onset type-2 diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2007;16(9):979-87.

Casscells SW, Granger E, Swedorske J, Goldhammer R, Shaheen M, Dorris J, et al. A comparison of select cardiovascular outcomes by antidiabetic prescription drug classes used to treat type 2 diabetes among Military Health System beneficiaries, fiscal year 2003-2006. *Am J Ther*. 2008;15(3):198-205.

Chang C-H, Toh S, Lin J-W, Chen S-T, Kuo C-W, Chuang L-M, et al. Cancer risk associated with insulin glargine among adult type 2 diabetes patients--a nationwide cohort study. *PLoS ONE* [Electronic Resource]. 2011;6(6):e21368.

Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375(9713):481-9.

Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. *PLoS Med*. 2009;6(9):e1000154.

Gosmanova EO, Canada RB, Mangold TA, Rawls WN, Wall BM. Effect of metformin-containing antidiabetic regimens on all-cause mortality in veterans with type 2 diabetes mellitus. *Am J Med Sci*. 2008;336(3):241-7.

Greenfield S, Billimek J, Pellegrini F, Franciosi M, De Berardis G, Nicolucci A, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study.[Summary for patients in Ann Intern Med. 2009 Dec 15;151(12):I54; PMID: 20008745]. *Ann Intern Med*. 2009;151(12):854-60.

Hayashi T, Kawashima S, Nomura H, Itoh H, Watanabe H, Ohrui T, et al. Age, gender, insulin and blood glucose control status alter the risk of ischemic heart disease and stroke among elderly diabetic patients. *Cardiovasc Diabetol*. 2011;10:86.

Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373(9681):2125-35.

Houlden R, Ross S, Harris S, Yale J-F, Sauriol L, Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral therapy in the management of Type 2 diabetes: the Canadian INSIGHT Study. *Diabetes Res Clin Pract*. 2007;78(2):254-8.

Iwamoto Y, Tajima N, Kadowaki T, Nonaka K, Taniguchi T, Nishii M, et al. Efficacy and safety of sitagliptin monotherapy compared with voglibose in Japanese patients with type 2 diabetes: a randomized, double-blind trial. *Diabetes Obes Metab*. 2010;12(7):613-22.

Jadzinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab*. 2009;11(6):611-22.

Karyekar C, Donovan M, Allen E, Fleming D, Ravichandran S, Chen R. Efficacy and safety of saxagliptin combination therapy in US patients with type 2 diabetes. *Postgrad Med*. 2011;123(4):63-70.

Komajda M, McMurray JJV, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J*. 2010;31(7):824-31.

Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care*. 2009;32(10):1789-95.

Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir I, et al. Database evaluation of the effects of long-term rosiglitazone treatment on cardiovascular outcomes in patients with type 2 diabetes. *J Clin Pharmacol*. 2011;51(2):173-80.

Loebstein R, Katzir I, Vasterman-Landes J, Halkin H, Lomnicky Y. Database assessment of the effectiveness of brand versus generic rosiglitazone in patients with type 2 diabetes mellitus. *Med Sci Monit*. 2008;14(6):CR323-6.

Monami M, Marchionni N, Masotti G, Mannucci E. Effect of combined secretagogue/biguanide treatment on mortality in type 2 diabetic patients with and without ischemic heart disease. *Int J Cardiol*. 2008;126(2):247-51.

Muramatsu T, Matsushita K, Yamashita K, Kondo T, Maeda K, Shintani S, et al. Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART Study. *Hypertension*. 2012;59(3):580-6.

Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2

diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. *Diabetes Obes Metab*. 2012;14(9):803-9.

Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol*. 2012;59(1):74-83.

Rosenstock J, Chou HS, Matthaei S, Seidel DK, Hamann A. Potential benefits of early addition of rosiglitazone in combination with glimepiride in the treatment of type 2 diabetes. *Diabetes Obes Metab*. 2008;10(10):862-73.

Saaristo T, Moilanen L, Korpi-Hyövälti E, Vanhala M, Saltevo J, Niskanen L, et al. Lifestyle Intervention for Prevention of Type 2 Diabetes in Primary Health Care: One-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D). *Diabetes Care*. 2010;33(10):2146-51.

Schwarz PE, Li J, Reimann M, Schutte AE, Bergmann A, Hanefeld M, et al. The Finnish Diabetes Risk Score is associated with insulin resistance and progression towards type 2 diabetes. *J Clin Endocrinol Metab*. 2009;94(3):920-6.

Singh KP, Periyandavar I, Rajadhyaksha GC, Jayaram S, Mishra AB, Kinagi S, et al. Evaluation of the efficacy, safety and tolerability of miglitol in adult Indian patients with uncomplicated type 2 diabetes mellitus. *J Indian Med Assoc*. 2007;105(6):344, 6, 50.

Song R, Ahn S, Roberts BL, Lee EO, Ahn YH. Adhering to a t'ai chi program to improve glucose control and quality of life for individuals with type 2 diabetes. *J Altern Complement Med*. 2009;15(6):627-32.

Suissa S, Azoulay L, Dell'Aniello S, Evans M, Vora J, Pollak M. Long-term effects of insulin glargine on the risk of breast cancer. *Diabetologia*. 2011;54(9):2254-62.

Toprani A, Fonseca V. Thiazolidinediones and congestive heart failure in veterans with type 2 diabetes.[Erratum appears in *Diabetes Obes Metab*. 2012 Apr;14(4):386]. *Diabetes Obes Metab*. 2011;13(3):276-80.

Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ*. 2009;339:b4731.

Duplicate data, used another source

Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-86.

Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011(6):CD008143.

Ramachandran A, Arun N, Shetty AS, Snehalatha C. Efficacy of primary prevention interventions when fasting and postglucose dysglycemia coexist: analysis of the Indian Diabetes Prevention Programmes

(IDPP-1 and IDPP-2). *Diabetes Care*. 2010;33(10):2164-8.

Rasmussen SS, Glumer C, Sandbaek A, Lauritzen T, Borch-Johnsen K. Progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screening programme in general practice: the ADDITION Study, Denmark. *Diabetologia*. 2007;50(2):293-7.

Reboldi G, Gentile G, Manfreda VM, Angeli F, Verdecchia P. Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes. *Curr Cardiol Rep*. 2012;14(1):89-96.

Woodward M, Patel A, Zoungas S, Liu L, Pan C, Poulter N, et al. Does glycemic control offer similar benefits among patients with diabetes in different regions of the world? Results from the ADVANCE trial. *Diabetes Care*. 2011;34(12):2491-5.

Wright JT, Probstfield JL, Cushman WC, Pressel SL, Cutler JA, Davis BR, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. *Arch Intern Med*. 2009;169(9):832-42.

Zoungas S, Chalmers J, Ninomiya T, Li Q, Cooper ME, Colagiuri S, et al. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia*. 2012;55(3):636-43.

Systematic review, used as source document only

Ahmed AA, Alsharief E, Alsharief A. Intensive versus conventional glycemic control: what is best for patients with type 2 diabetes? *Diabetes Metab Syndr*. 2013;7(1):48-51.

Baker MK, Simpson K, Lloyd B, Bauman AE, Singh MAF. Behavioral strategies in diabetes prevention programs: a systematic review of randomized controlled trials. *Diabetes Res Clin Pract*. 2011;91(1):1-12.

Chatterjee S, Sharma A, Lichstein E, Mukherjee D. Intensive glucose control in diabetics with an acute myocardial infarction does not improve mortality and increases risk of hypoglycemia-a meta-regression analysis. *Curr Vasc Pharmacol*. 2013;11(1):100-4.

Chen YH, Feng B, Chen ZW. Statins for primary prevention of cardiovascular and cerebrovascular events in diabetic patients without established cardiovascular diseases: a meta-analysis. *Exp Clin Endocrinol Diabetes*. 2012;120(2):116-20.

Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ*. 2012;184(12):E675-83.

Hemmingsen B, Schroll JB, Lund SS, Wetterslev J, Gluud C, Vaag A, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2013;4:CD009008.

Hopper I, Billah B, Skiba M, Krum H. Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovasc Prev Rehabil*. 2011;18(6):813-23.

Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and

cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2008;10(12):1221-38.

Monami M, Lamanna C, Marchionni N, Mannucci E. Rosiglitazone and risk of cancer: a meta-analysis of randomized clinical trials. *Diabetes Care*. 2008;31(7):1455-60.

Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque i Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2008(3).

Phung OJ, Sood NA, Sill BE, Coleman CI. Oral anti-diabetic drugs for the prevention of Type 2 diabetes. *Diabet Med*. 2011;28(8):948-64.

Yuen A, Sugeng Y, Weiland TJ, Jelinek GA. Lifestyle and medication interventions for the prevention or delay of type 2 diabetes mellitus in prediabetes: a systematic review of randomised controlled trials. *Aust N Z J Public Health*. 2010;34(2):172-8.

Randomized, Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
  - For 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.
- All important outcomes considered.
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

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; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with 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. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws 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. For RCTs, intention to treat analysis is lacking.

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 variables.

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.

Source: *U.S. Preventive Services Task Force Procedure Manual.* AHRQ Publication No. 08-05118-EF, July 2008. Available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm.

Appendix B1. Studies of Screening for DM

Author, Year	Study Design	No. of Centers Country	Screening Groups Described	Prevalence of Diabetes, if reported	Study Duration Followup	Baseline Demographics
Park 2008[91] ADDITION - Cambridge (pilot phase)	RCT	Two general practice sites United Kingdom	A. Invited to screening (n=116) A1. Screen-detected DM (n=6) A2. No DM diagnosed as a result of screening (n=89) B. Not invited to screening (n=238)	Prevalence in screened group at initial screening: 4.0% (5/116)	Study duration: NR Mean followup: 6 weeks	A vs B Mean age 58 vs 59 years 34% vs 36% female Race not reported
Rahman, 2012[92] Ely Cohort	RCT	Single center United Kingdom	A. Health assessment in diabetics who were previously screened (n=92) B. Health assessment in diabetics who were not previously screened (n=60)	Prevalence in screened group at initial screening: 3.0% (51/1,705)	Study duration: 12 years Mean followup: 11.6 years	A vs. B Mean age: 68 vs. 66 years 47% vs. 46% female Race not reported
Simmons, 2011[49] Ely Cohort	RCT	Single center United Kingdom	Phase 1 (1990-1999) A. Invited to screening with OGTT; rescreening at 5 and 10 years (n=1,705) A1. Attended screening (n=1,157/1,705; 68%) A2. Did not attend screening (n=548/1,705; 32%) B. No screening (n=3,231) Phase 2 (2000-2008) A. Invited to screening A1. Attended screening (n=714/1,577; 45%) A2. Did not attend screening (n=863/1,577; 55%) B. No screening (n=1,425)	Prevalence in screened group at initial screening: 3.0% (51/1,705)	Phase 1: Median followup 10 years Phase 2: Median followup 8 years	Screened vs. unscreened, entire cohort Mean age, females: 51 vs. 53 years (p<0.001) Mean age, males: 51 vs. 53 years (p<0.001) 49% vs. 55% female Race not reported
Simmons, 2012[67] ADDITION-Cambridge	RCT (cluster)	54 centers United Kingdom	A. Screening with intensive treatment or routine care (n=15,089) B. No screening (n=4,137)	A vs. B Unadjusted prevalence: 3.0% vs. 3.3%	Study duration: 4.2 years (January 2002-March 2006) Median followup: 9.6 years (IQR 8.9-9.9 years)	A vs. B Mean age 58 vs. 58 years 36% vs. 36% female Race not reported

Appendix B1. Studies of Screening for DM

Author, Year	Diabetes Risk	Inclusion and Exclusion Criteria	Screened, Eligible, Enrolled, Analyzed, Withdrawal, Loss to Followup	Results	Adverse Events	Funding Source
Park 2008[91] ADDITION - Cambridge (pilot phase)	A vs B Mean BMI 31.8 vs 31.3 kg/m^2 36% vs 38% use of antihypertensives	Age 40-69 years without known diabetes identified as being high-risk	Screened: 1,280 Eligible: 355 Enrolled: 355 Analyzed: 245 Withdrawal: unclear Loss to followup: 31% (110/355)	Not reported	A vs B STAI anxiety score (scale 20-80; higher score=more anxiety): 37.6 (SD 12.2) vs 34.1 (SD 12.1); p=0.015 Self-perceived health score (scale 1-5; higher score=better perceived health): 2.97 (SD 0.86) to 2.95 (SD 0.87); p=0.82 Illness representation subscales: no between group difference for any measure A1 vs A2 STAI anxiety score: 46.7 versus 37.0; p=0.03	Not reported
Rahman, 2012[92] Ely Cohort	A vs. B Mean BMI 30.4 vs. 29.7 kg/m^2 Mean HbA1c 7.0% vs. 7.4%	Men and women aged 40-65 years, free of known diabetes, able to leave house	Screened: 4,936 Eligible: NR Enrolled: 3,410 Analyzed: 152 (only those who progressed to diabetes) A vs. B Loss to followup: 21% (24/116) vs. 28% (23/83)	A vs B Self-reported MI: 7/92 vs 8/60; RR 0.57, 95% CI 0.22 to 1.49 Self-reported stroke: 3/92 vs 5/60; RR 0.39, 95% CI 0.10 to 1.58 Ischemic heart disease: 30/92 vs 28/60; RR 0.70, 95% CI 0.47 to 1.04 Nephropathy: 4/92 vs 1/60; RR 2.61, 95% CI 0.30 to 23) Peripheral neuropathy: 39/92 vs 32/60; RR 0.79, 95% CI 0.57 to 1.11 Peripheral vascular disease: 5/92 vs 2/60; RR 1.63, 95% CI 0.33 to 8.13 Mean SF-36 physical function score: 67.2 (SD 29.4) vs 69.6 (SD 30.7); p=0.64 Mean SF-36 mental health score: 77.8 (SD 16.5) vs 79.7 (SD 16.1); p=0.47		Medical Research Council; National Health Service R&D

Appendix B1. Studies of Screening for DM

Author, Year	Diabetes Risk	Inclusion and Exclusion Criteria	Screened, Eligible, Enrolled, Analyzed, Withdrawal, Loss to Followup	Results	Adverse Events	Funding Source
Simmons, 2011[49] Ely Cohort	NR	Men and women aged 40-65 years, free of known diabetes, able to leave house	Screened: 4,936 Eligible: NR Enrolled: 4,936 Analyzed: 4,936	Phase 1 A vs B All-cause mortality: HR 0.96, 95% CI 0.77 to 1.20; aHR 0.79 (95% CI 0.63 to 1.00) A1 vs B All-cause mortality: HR 0.64, 95% CI 0.47 to 0.86; aHR 0.54, 95% CI 0.40 to 0.74) A2 vs B All-cause mortality: HR 1.68, 95% CI 1.27 to 2.22; aHR 1.36, 95% CI 1.01 to 1.82 Phase 2 A vs B All-cause mortality: HR 1.20, 95% CI 0.95 to 1.51; aHR 1.18, 95% CI 0.93 to 1.51 A1 vs B All-cause mortality: HR 0.46, 95% CI 0.311 to 0.69; aHR 0.52, 95% CI 0.35 to 0.78 A2 vs B All-cause mortality: HR 1.85, 95% CI 1.45 to 2.36; aHR 1.73, 95% CI 1.34 to 2.24	NR	Medical Research Council; National Health Service R&D
Simmons, 2012[67] ADDITION-Cambridge	A vs. B BMI: 30.5 vs. 30.6 Median risk score: 0.35 vs. 0.34	Diabetes risk score of 0.17 or higher, not known to have diabetes Exclude: Pregnancy, lactation, an illness with a likely prognosis of less than a year, or a psychiatric illness likely to restrict study involvement or invalidate informed consent	Screened: 151,464 Eligible: 20,184 Enrolled: 19,226 Analyzed: unclear 3,352 (22%) did not participate in screening (declined or deemed unfit by practitioner)	A vs. B All-cause mortality: 1532/15089 vs 377/38126; HR 1.06 (95% CI 0.90 to 1.25) Cardiovascular mortality: 482/15089 vs 124/4137; HR 1.02 (95% CI 0.75 to 1.38) Cancer mortality rate: 697/15089 vs 169/4137; HR 1.08 (95% CI 0.90 to 1.30) Other causes of death: 353/15089 vs 84/4137; HR 1.10 (95% CI 0.87 to 1.39) Diabetes-related mortality: HR 1.26 (95% CI 0.75 to 2.10)	NR	Wellcome Trust; Medical Research Council; National Health Service R&D; National Institute for Health Research; University of Arhus, Denmark; Bio-Rad

Abbreviation: BMI = body mass index; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; MI = myocardial infarction; NR = not relevant; OGTT = oral glucose tolerance test; R&D = research and development; RCT = randomized, controlled trial; RR = relative risk; SD = standard deviation.

Appendix B2. Quality Assessment of Studies on Screening for DM

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze Persons in the Groups in Which They Were Randomized?	Quality Rating
Park 2008[91] ADDITION-Cambridge (pilot study)	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Fair
Simmons, 2012[67] ADDITION-Cambridge	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	No	Yes	Good
Simmons, 2011[49]; Rahman 2012[92] Ely	Unclear	Unclear	Differences in gender; age and deprivation; adjusted for in analysis	Yes	Unclear	No	No	Yes	No	Yes	Fair

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion/Exclusion Criteria
Andrews, 2013[95]	RCT	217 centers United Kingdom	A. Intensive diet and exercise (n=246) B. Intensive diet (n=248) C. Usual care (n=99)	Total followup: 1 year	**A vs B vs C** Mean age: 60 vs 60 vs 60 years Female sex: 36% vs 34% vs 37% Race: 94% vs 96% vs 97% White; other races not reported HbA1c: 6.7 vs 6.6 vs 6.7%	Age 30 to 80 years with DM diagnosis 5-8 months prior to study enrollment and HbA1c <10%, BP <180/100
Davies et al. 2008[96] and Khunti 2012[97] DESMOND Trial	Cluster RCT	13 primary care centers England, Scotland	A. Group intervention for 6 hrs within 12 weeks of diagnoses aimed at changing lifestyle (n=437) B. Control group (n=387)	Total followup: 3 years	**A vs B** Mean age: 59 vs 60 53% vs 57% male 94% vs 94% White Mean BMI 32.3 vs 32.4 kg/m^2	Diagnosis of DM within 4 weeks of study entry Exclude: Age <18 years, severe mental health problems; unable to participate in a group program, including due to language barrier; participation in another research study
DeFronzo, 2011[98]	RCT	8 centers United States	A. Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Median followup: 2.4 years	**A vs. B** Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% White, 26% Hispanic, 19% Black, 3% other vs. 57% White, 25% Hispanic, 15% Black, 3% other Mean BMI: 33.0 vs. 34.5 Mean HbA1c: 5.5 vs. 5.5	Patients 18 years or older with impaired glucose tolerance (fasting plasma glucose between 95 and 125 mg/dL), BMI ≥25, and at least one other risk factor for diabetes Exclude: Diabetes; previous treatment with thiazolidinedione (ever), metformin (within one year prior to randomization), or sulfonylureas, meglitinide, alpha glucosidase inhibitors, or insulin for more than one week within the prior year or within 3 months prior to randomization; cardiovascular disease, hospitalization for treatment of heart disease or stroke in past 6 months; NYHA class >2; left bundle branch block or third degree AV block; aortic stenosis; SBP >180 mmHg or DBP >105 mmHg; renal disease; anemia; hepatitis; gastrointestinal disease; recent or significant abdominal surgery; pulmonary disease with dependence on oxygen or daily use of bronchodilators; chronic infection; weight loss >10% of body weight in past 6 months; currently pregnant or <3 months postpartum; currently nursing or >6 weeks of having completed nursing; anticipated pregnancy; major psychotic disorders; excessive alcohol intake; thyroid disease; other endocrine disorders; fasting plasma triglyceride >400 mg/dL; history of bladder cancer; or hematuria at screening

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion/Exclusion Criteria
DREAM Trial Investigators 2008[99] See also: DREAM Trial Investigators, 2006a[14] and DREAM Trial Investigators, 2006b[15]	RCT (2X2 factorial design)	191 Centers 21 countries	A. Ramapril 15 mg/day (n=2623) B. Placebo (n=2646) C. Rosiglitazone 0.8mg/day (n=2635) D. Placebo (n=2634) *Patients randomized twice, to Ramapril or placebo and Rosiglitazone or placebo	Mean followup: 3 years	**A vs. B & C vs. D** Mean age: 55 vs. 55 years & 55 vs. 55 years Female sex: 59.7% vs. 58.7% & 58.3% vs. 60.1% Race: NR	Ages >30 yrs with IFG(6.1-7.0 mmol/L) and/or IGT by 2hr OGTT 7.8-11.0 mmol/L Exclude: LVEF < 40%, CHF, Documented CVD: ischemic heart disease, intermittent claudication, stroke, Uncontrolled Htn requiring ACE or ARB, Renal artery stenosis, Serum creatinine > 2.26 mg/dl, or creatinine clearance < 0.6 ml/s, or clinical proteinuria.
Florez, 2012[100] DPP	RCT	27 centers United States	A. Intensive lifestyle intervention, including diet and exercise to achieve modest weight reduction (n=1048) B. Metformin 850 mg/twice daily (n=1043) C. Placebo (n=1041)	Study duration: 5 years	**A vs. B vs. C** Mean age: 51 vs. 51 vs. 50 years Female sex: 68% vs. 66% vs. 69% Race: 54% White, 19% Black, 17% Hispanic, 9% Other vs. 56% White, 21% Black, 15% Hispanic, 8% Other vs. 54% White, 20% Black, 16% Hispanic, 10% Other Mean BMI: 33.9 vs. 33.9 vs. 34.2	Age ≥25 years, BMI ≥24 (≥22 in Asian Americans), fasting plasma glucose between 95 and 125 mg/dL, and IGT Exclude: Patients taking medication known to affect glucose tolerance or having illness likely to reduce life expectancy or ability to participate
Kawamori, 2009[101]	RCT	103 Japanese institutions	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Study duration: 5 years Mean followup: 3 years	**A vs. B** Mean age 55.7 vs. 55.7 years Female sex: 40% vs. 40% Race: NR	Ages 30-70, FPG <6.9 mmol/L, 2hr OGTT 7.8-11.0 mmol/L, hbA1c <6.5, and one RF from metabolic syndrome or FHx Exclude: diabetes and disease likely to impair GT
Li, 2008[102] and Li, 2014[110] Da Qing	RCT (cluster)	33 centers China	A. Combined lifestyle, diet, or lifestyle + diet diet interventions: increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time and physical activity (n=438) B. Control (n=138)	20 year followup of Da Qing study Mean followup: 9.4 years intervention weekly for 1m, monthly for 3 m and every 3months after that for remainder of the study (6 years)	**A vs. B** Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: NR Mean BMI: 25.7 vs. 26.2	Patients aged >25 years, with IGT Exclude: Not reported

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion/Exclusion Criteria
NAVIGATOR, 2010[103]	RCT	806 centers 40 countries	A. Nateglinide 60 mg/3 times daily (n=4645) B. Placebo (n=4661) *Patients also randomized in 2x2 factorial design to receive valsartan or placebo	Median followup 5 years	**A vs. B** Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% White, 2.6% Black, 6.7% Asian, 7.8% other vs. 83.2% White, 2.5% Black, 6.5% Asian, 7.8% other Mean BMI: 30.5 vs. 30.5 HbA1c: 5.8 vs. 5.8	Patients with IGT, fasting plasma glucose between 95 and 126 mg/dL, and one or more cardiovascular risk factor or known cardiovascular disease (for subjects aged ≥55 years) Exclude: Patients who had taken antidiabetic medication in the prior 5 years, had abnormal laboratory test results, or had concomitant conditions that could interfere with assessment
NAVIGATOR, 2010[104]	RCT	806 centers 40 countries	A. Valsartan 160 mg/once daily (n=4631) B. Placebo (n=4675) *Patients also randomized in 2x2 factorial design to receive nateglinide or placebo	Median followup 5 years	**A vs. B** Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83.1% White, 2.4% Black, 6.4% Asian, 8.0% other vs. 83.1% White, 2.6% Black, 6.7% Asian, 7.5% other Mean BMI: 30.4 vs. 30.6 HbA1c: 5.8 vs. 5.8	Patients with IGT, fasting plasma glucose between 95 and 126 mg/dL, and one or more cardiovascular risk factor or known cardiovascular disease (for subjects aged >55 years) Exclude: Patients who had taken antidiabetic medication in the prior 5 years, had abnormal laboratory test results, or had concomitant conditions that could interfere with assessment
Nijpels, 2008[105] DAISI	RCT	Single center The Netherlands	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	3 years	**A vs. B** Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race: NR Mean BMI: 28.4 vs. 29.5 HbA1c: 5.9 vs. 5.6	Patients aged 45 to 70 years, with fasting plasma glucose ≥7.8 mmol/L, a 2-hour plasma glucose of 8.6-11.1 mmol/L, and HbA1c≤7.0 Exclude: Patients who failed to complete the 6-week qualification period, in which acarbose doses were up-titrated over three weeks to 50 mg/three times daily and maintained for three weeks
Ramachandran, 2009[106] IDPP-2	RCT	Clinics in India enrolled patient from railway and electric industry	A. Pioglitazone (n=181) B. Placebo (n=186)	Mean follow up 3 years	**A vs. B** Mean age 45.1 vs. 45.5 Female sex: 13% vs. 14% Race: NR	Ages 35-55, IGT 7.8-11.1 mmol/L Exclude: coronary artery disease, stroke history, major Q wave abnormality, liver disorders, kidney disorders

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion/Exclusion Criteria
Uusitupa, 2009[108] Finnish DPS	RCT	5 centers Finland	A. Intensive diet and counseling group (n=257) B. Control group (n=248) C. Normal FINDRISK Cohort (n=1570) D. IGT FINDRISK Cohort (n=183) E. Screen-detected FINDRISK Cohort (n=59) F. Previously diagnosed FINDRISK Cohort (n=69)	**A and B**: 10.6 yrs **C-F**: 13.8 yrs	**A vs. B vs. C vs. D vs. E vs. F** Mean age:55.4 vs. 55.0 vs. 53.7 vs. 55.8 vs. 55.9 vs. 55.6 Female sex: 66% vs. 68% vs. 59% vs. 49% vs. 45% vs. 49% Race: NR BMI: 31.4 vs. 31.2 vs. 26.8 vs. 29.8 vs. 31.7 vs. 30.5	Age 40-64, BMI >25, 2 -2hr OGTT with IGT result according to WHO 1985 criteria Exclude: Recent within 6 m CVD event
Zinman, 2010[109] CANOE	RCT	2 centers Canada	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed dose combination (n=103) B. Placebo (n=104)	Median followup: 3.9 years	**A vs. B** Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 74.8% White, 7.8% South Asian, 6.8% Latino, 10.7% other vs. 74% White, 6.8% South Asian, 6.7% Latino, 12.5% other Mean BMI: 31.3 vs. 32.0	Residents of Ontario, Canada, aged 30 to 75 years (18 to 75 years for those of Canadian native ancestry), with at least one risk factor for diabetes, diagnosed with IGT based on fasting plasma glucose test and OGTT Exclude: Current use of metformin or rosiglitazone, previous use of an anti-diabetes medication (except to treat gestational diabetes), significant hepatic disease, or renal dysfunction

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Number Screened, Eligible, Enrolled, and Analyzed; Withdrawals; Loss to Followup	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Andrews, 2013[95]	Screened: 1,634 Eligible: 712 Enrolled: 593 Analyzed: 593 Withdrawals: 0.3% (2/593) Loss to followup: 11% (66/593)	**A vs B vs C** Mortality: 0% (0/246) vs 0% (0/248) vs 1%(1/99); A vs C: RR 0.14 (95% CI 0.01 to 3.31); B vs C: RR 0.14 (95% CI 0.01 to 3.29)	NR	Good	Diabetes UK and UK Department of Health
Davies et al. 2008[96] and Khunti 2012[97] DESMOND Trial	Screened: 1,109 Eligible: 1,053 Enrolled: 824 Analyzed: 604 (3 years) Withdrawals: 5% (44/824)	**A vs B** Quality of life, WHOQOL-BREF – Overall satisfaction with quality of life: 4.0 vs. 4.0; p=0.48 Overall satisfaction with health: 4.0 vs. 4.0; p=0.94	**A vs B** All-cause withdrawals: 21/437 (5%) vs 23/387 (6%); RR 0.81 (95% CI 0.45 to 1.44)	Fair	Diabetes UK
DeFronzo, 2011[98]	Screened: 1827 Eligible: NR Enrolled: 602 Analyzed: 602 **A vs. B** Withdrawal: 29.7% (90/303) vs. 23.7% (71/299) Loss to followup: 9.2% (28/303) vs. 7.4% (22/299)	**A vs. B** Mortality: 1.0% (3/303) vs. 0.3% (1/299); RR 2.96, 95% CI 0.31 to 28.30 Cardiovascular events: 26 vs. 23 Nonfatal MI: 2 vs. 1 TIA: 1 vs. 1 CAD w/o revascularization: 2 vs. 1 CABG : 2 vs. 6	**A vs. B** Any adverse event: 49.8% (151/303) vs. 40.5% (121/299); RR 1.23, 95% CI 1.03 to 1.47	Fair	Takeda Pharmaceuticals
DREAM Trial Investigators 2008[99] See also: DREAM Trial Investigators, 2006a[14] and DREAM Trial Investigators, 2006b[15]	Screened: 24872 Randomized: 5269	**A vs. B & C vs. D** Cardiovascular composite events incidence: 2.6% (69/2623) vs. 2.4% (64/2646); HR 1.09, 95% CI 0.78 to 1.53 & 2.9% (77/2635) vs. 2.1% (56/2634); HR 1.38, 95% CI 0.98 to 1.95 Cardiovascular death: 0.5% (12/2623) vs. 0.4% (10/2646); HR 1.21, 95% CI 0.52 to 2.80 & 0.5% (12/2635) vs. 0.4% (10/2634); HR 1.20, 95% CI 0.52 to 2.77 MI: 0.5% (14/2623) vs. 0.4% (11/2646); HR 1.29, 95% CI 0.59 to 2.84 & 0.6% (16/2635) vs. 0.3% (9/2634); HR 1.78, 95% CI 0.79 to 4.03 Stroke: 0.2% (4/2623) vs. 0.3% (8/2646); HR 0.50, 95% CI 0.15 to 1.66 & 0.3% (7/2635) vs. 0.2% (5/2634); HR 1.40, 95% CI 0.44 to 4.40 Congestive heart failure: 0.5% (12/2623) vs. 0.2% (4/2646); HR 3.06, 95% CI 0.99 to 9.48 & 0.5% (14/2635) vs. 0.1% (2/2634); HR 7.04, 95% CI 1.60 to 31.0 Revascularization: 1.1% (28/2623) vs. 1.4% (38/2646); HR 0.74, 95% CI 0.46 to 1.21 & 1.4% (37/2635) vs. 1.1% (29/2634); HR 1.27, 95% CI 0.78 to 2.07 Cardiovascular death, MI, stroke: 1% (27/2623) vs. 1.1% (29/2646); HR 0.94, 95% CI 0.56 to 1.59 & 1.3% (33/2635) vs. 0.9% (23/2634); HR 1.43, 95% CI 0.84 to 2.44 Total Mortality: 1.2% (31/2623) vs. 1.2% (32/2646); HR 0.98, 95% CI 0.60 to 1.61 & 1.1% (30/2635) vs. 1.3% (33/2634); HR 0.91, 95% CI 0.56 to 1.49	NR	Good	Canadian Institute of Health Research; Aventis Pharma; GalaxoSmithKline; King Pharmaceuticals; Wyeth Ayerst

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Number Screened, Eligible, Enrolled, and Analyzed; Withdrawals; Loss to Followup	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Florez, 2012[100] DPP	Screened: NR Eligible: NR Enrolled: 3,234 Analyzed: 3,132	**A vs. C** Quality of life, SF-36 score changes from baseline, mean between-group difference: SF-6D: 0.0084 (SD 0.0041; p<0.05) PCS: 1.57 (SD 0.30; p<0.01) MCS: -0.29 (SD 0.32; p=NS) Physical function: 3.58 (SD 0.66; p<0.01) Body pain: 1.93 (SD 0.78; p<0.01) General health: 3.23 (SD 0.66; p<0.01) Vitality: 2.05 (SD 0.77; p<0.01) **B vs. C** Quality of life, SF-36 score changes from baseline, mean between-group difference: SF-6D: 0.0019 (SD 0.0041; p=NS) PCS: 0.15 (SD 0.30; p=NS) MCS: 0.22 (SD 0.32; p=NS) Physical function: 0.13 (SD 0.71; p=NS) Body pain: 0.50 (SD 0.78; p=NS) General health: 0.06 (SD 0.66; p=NS) Vitality: 0.09 (SD 0.76; p=NS) *No measure in either group reached clinically meaningful difference of 3%*		Good	National Institute of Diabetes and Digestive and Kidney Diseases; Office of Research on Minority Health; National Institute of Child Health and Human Development; National Institute on Aging; Centers for Disease Control and Prevention
Kawamori, 2009[101]	Screened: 4582 Eligible: NR Enrolled: 1780 Analyzed: 1778 **A vs. B** Withdrawal: 14.4% (129/897) vs. 16.5% (146/883)	**A vs. B** Death 0.7% (6/897) including 1 MI vs. 0% (0/881); RR 12.77, 95% CI 0.72 to 226.32	**A vs. B** Withdrawal due to adverse events: 7.4% (66/897) vs. 6.2% (55/883) Any adverse event: 90% (810/897) vs. 85% (750/881 Serious adverse event: 0.6% (5/897) vs. 0.2% (2/881)	Good	Takeda Pharmaceuticals

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Number Screened, Eligible, Enrolled, and Analyzed; Withdrawals; Loss to Followup	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Li, 2008[102] and Li, 2014[110] Da Qing	Screened: 110,660 Eligible: NR Enrolled: 577 Analyzed: 530 Withdrawal: 7 Loss to followup: 40	**A vs. B** <u>20-year followup</u> All-cause mortality: 25% (110/438) vs. 29% (40/138); HR 0.96, 95% CI 0.65 to 1.41 CVD mortality: 13% (57/438) vs 17% (23/138); HR 0.83, 95% CI 0.48 to 1.40 CVD event incidence: 41% (180/438) vs 44% (61/138); HR 0.98, 95% CI 0.71 to 1.37 <u>23-year followup</u> All-cause mortality: 28% (121/430) vs. 38% (53/138); HR 0.71 (95% CI 0.51 to 0.99) -Women: 15% (31/205) vs 29% (17/59); HR 0.46 (95% CI 0.24 to 0.87) -Men: 40% (93/233) vs 46% (36/79); HR 0.97 (95% CI 0.65 to 1.46) CVD mortality: 12% (51/430) vs. 20% (27/138); HR 0.59 (95% CI 0.36 to 0.96) -Women: 6% (12/206) vs 17% (10/59); HR 0.28 (95% CI 0.11 to 0.71) -Men: 17% (40/233) vs 22% (17/79); HR 0.91 (95% CI 0.50 to 1.65)	NR	Fair	World Health Organization, Centers for Disease Control and Prevention, China-Japan Friendship Hospital, and Da Qing First Hospital
NAVIGATOR, 2010[103]	Screened: 43502 Eligible: 9518 Enrolled: 9518 Analyzed: 9306 **A vs. B** Withdrawal: 3.5% (163/4645) vs. 3.1% (143/4661) Loss to followup: 9.6% (446/4645) vs. 9.8% (459/4661)	**A vs. B** Extended cardiovascular events: 25.6 vs. 27.5 cases/1000 person-years; HR 0.93, 95% CI 0.83 to 1.03 CVD death: 4.4 vs. 4.1 cases/1000 person-years; HR 1.07, 95% CI 0.83 to 1.38 All-cause mortality: 10.9 vs. 11 cases/1000 person-years; HR 1.00, 95% CI 0.85 to 1.17	**A vs. B** Discontinued due to adverse event: 11.2% (520/4645) vs. 10.4% (485/4661); RR 1.08, 95% CI 0.96 to 1.21 Hypoglycemia: 19.6% (911/4645) vs. 11.3% (527/4661); RR 1.73, 95% CI 1.57 to 1.92	Good	Novartis Pharma
NAVIGATOR, 2010[104]	Screened: 43502 Eligible: 9518 Enrolled: 9518 Analyzed: 9306 **A vs. B** Withdrawal: 3.3% (151/4631) vs. 3.3% (155/4675) Loss to followup: 9.4% (437/4631) vs. 10.0% (468/4675)	**A vs. B** Extended cardiovascular events: 26.2 vs. 26.9 cases/1000 person-years; HR 0.96, 95% CI 0.86 to 1.07 CVD death: 4.5 vs. 4.1 cases/1000 person-years; HR 1.09, 95% CI 0.85 to 1.40 All-cause mortality: 10.4 vs. 11.5 cases/1000 person-years; HR 0.90, 95% CI 0.77 to 1.05	**A vs. B** Discontinued due to adverse event: 12.0% (556/4631) vs. 11.4% (531/4675); RR 1.06, 95% CI 0.95 to 1.18 Hypoglycemia: 42.4% (1936/4631) vs. 35.9% (1678/4675); RR 1.16, 95% CI 1.11 to 1.23	Good	Novartis Pharma

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Number Screened, Eligible, Enrolled, and Analyzed; Withdrawals; Loss to Followup	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Nijpels, 2008[105] DAISI	Screened: 6651 Eligible: 171 Enrolled: 118 (53 failed qualification period) Analyzed: 118 **A vs. B** Loss to followup: 0% vs. 1.7% (1/58)	**A vs. B** Death: 1.7% (1/60) vs. 5.2% (3/58); RR 0.32, 95% CI 0.03 to 3.01	**A vs. B** Withdrawal due to adverse events: 36.7% (22/60) vs. 13.8% (8/58); RR 2.66, 95% CI 1.29 to 5.48	Fair	Bayer Healthcare AG
Ramachandran, 2009[106] IDPP-2	Screened: 6589 Enrolled: 407 Analyzed: 367 **A vs. B** Loss to followup: 11.3% (21/181) vs. 8.4% (16/186)	**A vs. B** Death: 1% (2/204) due to cardiac arrest vs. 0.5% (1/203) due to road accident; RR 1.99, 95% CI 0.18 to 21.78 Occurrence of heart disease requiring admission: 1% (2/204) vs. 0.5% (1/203); RR 1.99, 95% CI 0.18 to 21.78	**A vs. B** Major other adverse events: 2% (4/204) vs.4.9% (10/203); RR 0.40, 95% CI 0.13 to 1.25	Fair	India's Diabetes Research Foundation
Uusitupa, 2009[108] Finnish DPS	522 enrolled 17 patients not analyzed because did not consent for linkage records	**A vs. B vs. C vs. D vs. E vs. F** Death: 2.2 vs.3.8 vs. 6.6 vs.16.4 vs. 21.0 vs. 28.8 cases/1000 person-years Total mortality, unadjusted: HR 0.15, 95% CI 0.06 to 0.35 vs. HR 0.26, 95% CI 0.13 to 0.52 vs. HR 0.40, 95% CI 0.28 to 0.57 vs. HR 1 (reference standard) vs. HR 1.29, 95% CI 0.71 to 0.24 vs. HR 1.77, 95% CI 1.05 to 2.98 Total mortality, adjusted: HR 0.21, 95% CI 0.09 to 0.52 vs. HR 0.39, 95% CI 0.20 to 0.79 vs. HR 0.52, 95% CI 0.36 to 0.74 vs. HR 1 (reference standard) vs. HR 1.08, 95% CI 0.56 to 2.06 vs. HR 1.96, 95% CI 1.15 to 3.34 CVD event: 22.9 vs. 22.0 vs. 19.3 vs. 39.9 vs. 62 vs. 67.2 cases/1000 person-years CVD event, unadjusted: HR 0.59, 95% CI 0.41 to 0.83 vs. HR 0.56, 95% CI 0.40 to 0.80 vs. HR 0.48, 95% CI 0.37 to 0.62 vs. HR 1 (reference standard) vs. HR 1.58, 95% CI 1.04 to 2.39 vs. HR 1.69, 95% CI 1.11 to 2.39 CVD event, adjusted: HR 0.89, 95% CI 0.62 to 1.27 vs. HR 0.87, 95% CI 0.60 to 1.27 vs. HR 0.67, 95% CI 0.51 to 0.88 vs. HR 1 (reference standard) vs. HR 1.39, 95% CI 0.90 to 2.15 vs. HR 1.64, 95% CI 1.02 to 2.15	NR	Fair	multiple public and private funders

Appendix B3. Studies of the Effect of Interventions for Screen-Detected and Early DM, IFG, or IGT on Health Outcomes

Author, Year	Number Screened, Eligible, Enrolled, and Analyzed; Withdrawals; Loss to Followup	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Zinman, 2010[109] CANOE	Screened: 992 Eligible: 247 Enrolled: 207 Analyzed: 207 **A vs. B** Withdrawal: 12.6% (13/103) vs. 9.6% (10/104) Loss to followup: 1.9% (2/103) vs. 1.9% (2/104)	**A vs. B** MI: 0% (0/103) vs. 1% (1/104), RR 0.34, 95% CI 0.01 to 8.17 CHF: 0% (0/103) vs. 1% (1/104), RR 0.34, 95% CI 0.01 to 8.17	**A vs. B** Hypoglycemia: 2% (2/103) vs. 1% (1/104); RR 2.02, 95% CI 0.19 to 21.93	Good	GlaxoSmithKline

Abbreviations: AV = atrioventricular; BMI = body mass index; CABG = coronary artery bypass surgery; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; FHx = family history; FPG = fasting plasma glucose; GT = glucose tolerance; HbA = glycated hemoglobin; Hg= hemoglobin; 2HPG = 2-hour plasma glucose; HR = hazard ratio; IGT = impaired glucose tolerance; IRR = incident rate ratio; MCS = mental composite score; MI = myocardial infarction; NR = not relevant; NYHA = New York Heart Association; OGTT = oral glucose tolerance test; PCS = physical composite score; RCT = randomized, controlled trial; RF = risk factor; RR = relative risk; SBP = systolic blood pressure; SF = short form; TIA = transient ischemic attack; WHO = World Health Organization; WHOQOL-BREF = World Health Organization Quality of Life Assessment, short version.

Appendix B4. Quality Assessment of Studies of Interventions for Screen-Detected and Early DM, IFG, or IGT

Author, Year	Random-ization Adequate?	Allocation Conceal-ment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze Persons in the Groups in Which They Were Randomized?	Quality Rating
Andrews, 2013[95]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No/No	Yes	Good
Davies, 2008[96] DESMOND	Yes	Yes	No; not HbA1c, sex, or use of oral hypoglycemic agents	Yes	Yes	No	No	Yes	No/No	Yes	Fair
DeFronzo, 2011[98] ACT NOW	Unclear; likely yes (block randomization based on a 'randomization code')	Unclear	Yes	Yes	Unclear	Unclear; likely yes	Unclear; likely yes	Yes	No/No	Yes	Fair
DREAM trial investigators, 2008[99]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes; in previous paper	No/No	Yes	Good
Florez, 2012[100]	Unclear; Likely Yes	Unclear; Likely Yes	Yes	Yes	Yes	No; Yes for pharma-cologic interventions	No; Yes for pharma-cologic inter-ventions	Yes	No/No	Yes	Good
Kawamori, 2009[101]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Li, 2014[110] Da Qing	Unclear; cluster randomization	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
NAVIGATOR, 2010[103, 104]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Nijpels, 2008[105] DAISI	Yes	Yes	No; not HbA1c	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
Ramachandran, 2009[106] IDPP-2	Yes	No-sequential	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	No; ~11% randomized but not analyzed	Fair
Uusitupa, 2009[108]	Yes for DPS	Yes	DPS (Yes) FINRISK had different baseline characteristics	Yes	Yes	No	No	Yes	No/No	No	Fair

Appendix B4. Quality Assessment of Studies of Interventions for Screen-Detected and Early DM, IFG, or IGT

Author, Year	Random-ization Adequate?	Allocation Conceal-ment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze Persons in the Groups in Which They Were Randomized?	Quality Rating
Zinman, 2010[109] CANOE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good

Appendix B5. Harms of Interventions for Screen-Detected and Early DM, IFG, or IGT

Author, Year Study Name	Study Design	Setting Country Population	Interventions	Study Duration Mean Followup	Baseline Demographics	Adverse Events	Quality Rating	Funding Source
Lifestyle interventions								
Davies et al. 2008[96] and Khunti 2012[97] DESMOND Trial	Cluster RCT	13 primary care centers England, Scotland DM	A. Group intervention for 6 hrs within 12 weeks of diagnoses aimed at changing lifestyle (n=437) B. Control group (n=387)	Median followup 12 months	**A vs B** Mean age: 59 vs 60 53% vs 57% male 94% vs 94% White Mean BMI 32.3 vs 32.4 kg/m^2	**A vs B** All-cause withdrawals: 21/437 (5%) vs 23/387 (6%); RR 0.81 (95% CI 0.45 to 1.44)	Fair	Diabetes UK; Novonordisk educational grant; Hospital Trust from UH Leicester
Saito, 2011[107]	RCT	38 hospitals and clinic centers Japan IFG	A. Individual session and goal to decrease BW by 5% with follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. One session advise to reduce BW by 5% (n=311)	Study duration: 3 years Mean followup: 2.7 years	**A vs. B** Mean age 50 vs 48 years 72% vs 71% male Race not reported Mean BMI 26.9 vs 27.1 kg/m^2 Mean HbA1c 5.4% vs 5.4%	**A vs B** Serious adverse events: 0/330 (0%) vs 0/311 (0%); RR 0.94 (95% CI 0.02 to 47)	Fair	All Japan Federation of Social Insurance Associations
Pharmacologic interventions								
Metformin								
Diabetes Prevention Program, 2012[179]	RCT	27 clinics United States IGT	A. Metformin 850 mg/twice daily (n=1,073) B. Placebo (n=1,082)	Mean blinded treatment duration: 3.2 years Open-label lifestyle intervention: 6 month lifestyle intervention and 7-8 years additional followup	**A vs. B** Mean age: 50.9 vs. 50.3 years Female sex: 66.2 vs. 69.0% Race: 56% White, 21% Black, 15% Hispanic, 5% American Indian, 3% Asian vs. 54% White, 20% Black, 16% Hispanic, 6% American Indian, 5% Asian Mean BMI: 33.9 vs. 34.2 Mean HbA1c: 5.9% vs. 5.9%	**A vs. B** Non-serious hypoglycemia: 0.7% (7/1,073) vs. 0.7% (8/1,082) Serious anemia: 0.2% (2/1,073) vs. 0.1% (1/1,082) Serious lactic acidosis: 0% vs. 0% Serious hypoglycemia: 0% vs. 0%	Good	National Institute of Diabetes and Digestive and Kidney Diseases
TZDs								
DeFronzo, 2011[98]	RCT	8 centers United States IGT	A. Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Median followup 2.4 years	**A vs. B** Mean age 53 vs. 52 years 42% vvs 42% male 51% vs 57% White, 26% vs 25% Hispanic, 19% vs 15% Black 3% vs 3% other Mean BMI 33.0 vs 34.5 kg/m^2 Mean HbA1c 5.5% vs. 5.5%	**A vs. B** Any adverse event: 151/303 (50%) vs. 121/299 (42%); RR 1.23 (95% CI 1.03 to 1.47) Cancer: 3/303 (1%) vs 8/299 (3%); RR 0.37 (95% CI 0.10 to 1.38)	Fair	Takeda Pharmaceuticals

Appendix B5. Harms of Interventions for Screen-Detected and Early DM, IFG, or IGT

Author, Year Study Name	Study Design	Setting Country Population	Interventions	Study Duration Mean Followup	Baseline Demographics	Adverse Events	Quality Rating	Funding Source
DREAM Trial Investigators 2008[99]	RCT	191 Centers21 countries	A. Rosiglitazone 0.8mg/day (n=2635)B. Placebo (n=2634)	Mean follow up: 3 years	**A vs. B & C vs. D**Mean age 55 vs. 55 years58.3% vs. 60.1% femaleRace: NR	**A vs B**Congestive heart failure: 0.5% (14/2635) vs. 0.1% (2/2634); HR 7.04, 95% CI 1.60 to 31.0	Good	Canadian Institute of Health Research; Aventis Pharma; GalaxoSmithKline; King Pharmacuticals; Wyeth Ayerst
Ramachandran, 2009[106] IDPP-2	RCT	Community recruited India IGT	A. Pioglitazone (n=181) B. Placebo (n=186)	Mean follow up 3 years	**A vs. B** Mean age 45 vs 46 years 87% vs 86% male Race not reported Mean BMI 26.0 vs 26.2 kg/m^2 Mean HbA1c 5.8% vs 5.8%	**A vs. B** Serious adverse events: 4/181 (2%) vs 10/186 (5%); RR 0.41 (95% CI 0.13 to 1.29)	Fair	India's Diabetes Research Foundation
Alpha-glucosidase inhibitors								
Kawamori, 2009[101]	RCT	103 centers Japan IGT	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Study duration: 5 years Mean followup: 3 years	**A vs. B** Mean age 56 vs 56 years 60% vs 60% male Race not reported Mean BMI 25.8 vs 25.9 kg/m^2 Mean FPG 5.8 vs 5.9 mmol/L	**A vs. B** Withdrawal due to adverse events: 66/897 (7%) vs 55/883 (6%); RR 1.18 (95% CI 0.84 to 1.67) Serious adverse event: 5/897 (0.6%) vs 2/881 (0.2%); RR 2.46 (95% CI 0.48 to 13) Any adverse event: 810/897 (90%) vs. 750/881 (85%); RR 1.06 (95% CI 1.02 to 1.10)	Good	Takeda Pharmaceuticals
Nijpels, 2008[105] DAISI	RCT	Single center The Netherlands IGT	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	3 years	**A vs. B** Mean age 59 vs 57 years 51% vs 50% male Race not reported Mean BMI 28.4 vs. 29.5 kg/m^2 Mean HbA1c 5.9% vs. 5.6%	**A vs. B** Withdrawal due to adverse events: 22/60 (37%) vs. 8/58 (14%); RR 2.66 (95% CI 1.29 to 5.48)	Fair	Bayer Healthcare AG

Appendix B5. Harms of Interventions for Screen-Detected and Early DM, IFG, or IGT

Author, Year Study Name	Study Design	Setting Country Population	Interventions	Study Duration Mean Followup	Baseline Demographics	Adverse Events	Quality Rating	Funding Source
Nateglinide and Valsartan								
NAVIGATOR Study Group, 2010[103] NAVIGATOR	RCT	806 centers 40 countries IGT	A. Nateglinide 60 mg/3 times daily (n=4645) B. Placebo (n=4661)	Median followup 5 years	**A vs. B** Mean age 64 vs 64 years 50% vs 49% male 83% vs 83% White 2% vs 3% Black 6% vs 7% Asian 8.0% vs 8% other Mean BMI 30.4 vs 30.6 kg/m^2 Mean HbA1c 5.8% vs 5.8%	**A vs. B** Withdrawals due to adverse events: 520/4645 (11%) vs 485/4661 (10%); RR 10.8 (95% CI 0.96 to 1.21) Hypoglycemia: 911/4645 (20%) vs 527/4661 (11%); RR 1.73 (95% CI 1.57 to 1.92)	Good	Novartis Pharma
NAVIGATOR, 2010[104]	RCT	806 centers 40 countries IGT	A. Valsartan 160 mg/once daily (n=4631) B. Placebo (n=4675)	Median followup 5 years	**A vs. B** Mean age 64 vs 64 years 50% vs 49% male 83% vs 83% White 2% vs 3% Black 6% vs 7% Asian 8.0% vs 8% other Mean BMI 30.4 vs 30.6 kg/m^2 Mean HbA1c 5.8% vs 5.8%	**A vs. B** Withdrawals due to adverse events: 556/4631 (12%) vs. 531/4675 (11%); RR 1.06 (95% CI 0.95 to 1.18) Hypotension-related adverse events: 1936/4631 (42%) vs 1678/4675 (36%); RR 1.16 (95% CI 1.11 to 1.23)	Good	Novartis Pharma
Combination pharmacologic interventions								
Zinman 2010[109] CANOE	RCT	2 centers Canada IGT	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed dose combination (n=103) B. Placebo (n=104)	Median followup 3.9 years	**A vs. B** Mean age 50 vs 55 years 35% vs 32% male 75% vs 74% White 8% vs 7% South Asian 7% vs 7% Latino 11% vs 13% other Mean BMI 31.3 vs. 32.0 kg/m^2	**A vs B** Withdrawals due to adverse events: 4/103 (4%) vs 7/104 (7%); RR 0.58 (95% CI 0.17 to 1.91) Cancer: 2/103 (2%) vs 1/104 (1%); RR 2.02 (95% CI 0.19 to 22) Hypoglycemia: 1/103 (1%) vs 1/104 (1%); RR 1.01 (95% CI 0.06 to 16)	Good	GlaxoSmithKline

Abbreviations: AG = alpha-glucosidase; BMI = body mass index; BW = body weight; CANOE = Canadian Normoglycemia Outcomes Evaluation; CI = confidence interval; CVD = cardiovascular disease; DAISI = Diabetes Autoimmunity Study; DESMOND = diabetes education and self management for ongoing and newly diagnosed; DM = diabetes mellitus; FPG - fasting plasma glucose; HbA = glycated hemoglobin; Hg= hemoglobin; IDPP = Indian Diabetes Prevention Program; IGT = impaired glucose tolerance; MMOL = blood glucose meters; RCT = randomized, controlled trial; RR = relative risk.

Appendix B6. Study Characteristics of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year	Purpose of Study	Databases Searched, Date of Last Search	Number of Studies	Types of Studies Included
Intensive glucose control				
Buehler, 2013[114] *Good*	Examine the effect of tight versus conventional glucose control in people with DM	Cochrane library, MEDLINE, EMBASE, ISI Web of Knowledge through May 2011	6 RCTs	Trials comparing tight versus conventional glucose control conducting in people age ≥18 years with DM and followup ≥1 year
Hemmingsen, 2012[115] *Good*	Assess the effects of targeting intensive versus standard glycemic control in people with DM	Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, CINAHL through December 2010	20 RCTs	Trials that prespecified different targets of glycemic control in adults with DM.
Coca, 2012[116] *Good*	Compare the effects of intensive glucose control and standard glucose control on renal events in people with DM	MEDLINE, EMBASE, CCRCT through December 2010	7 RTCs	Trials comparing surrogate renal end points and clinical renal end points in patients with DM receiving intensive glucose control vs those receiving standard glucose control.
Hemmingsen, 2011[117]	Assess the effect of intensive versus standard glycemic control on all-cause and CV mortality, non-fatal MI, microvascular complications and severe hypoglycemia	Cochrane Library, MEDLINE, EMBASE, Science Citation Expanded Index, LILACS, CINAHL through December 2010. Hand searches of reference lists, conference proceedings, pharmaceutical companies, FDA	14 RCTs	Trials comparing targeted intensive glycemic control with standard glycemic control in patients with DM. Published and unpublished trials in all languages were included, irrespective of predefined outcomes.
Boussageon, 2011[118] *Good*	To determine all-cause mortality and deaths from cardiovascular events related to intensive glucose lowering treatment in people with DM	MEDLINE, EMBASE, CDSR through July 2010	13 RCTs	Trials that assessed the effect of intensive glucose lowering treatment on CV and microvascular events
Castagno, 2011[119] *Good*	To determine whether improved glycemic control reduces the risk of heart failure.	PubMed, CCRCT, metaRegister, pre-MEDLINE, and CINAHL through October 2010	8 RCTs	Trials comparing strategies of more versus less intensive glucose-lowering reporting HF events.
Wu, 2010[120] *Good*	To evaluate the efficacy of intensive glucose control in the prevention of cardiovascular events when compared with standard glucose controls	MEDLINE, EMBASE, the Cochrane Library, and Science Citation Index through January 2009	6 RCTs	Trials comparing intensive glucose control strategies and standard glucose control strategies in populations with DM reporting all-cause and CV mortality and macrovascular events
Kelly, 2009[121] *Good*	To summarize clinical benefits and harms of intensive versus standard glucose control for people with DM	MEDLINE database through April 2009 with no language restrictions.	5 RCTs	Trials comparing intensive glucose control with standard glucose control with prespecified glucose targets, reporting CVD as the primary outcome and n>500
Ma, 2009[123] *Good*	To assess the relationship between major vascular events and intensive glycemic control	MEDLINE, EMBASE through December 2008, and the Cochrane Library, Issue 4, 2008	8 RCTs	Trials comparing intensive and standard glycemic control reporting vascular events, with target HbA1c levels
Mannucci, 2009[124] *Good*	To assess of the effects of improvement of glycemic control on the incidence CVD	MEDLINE, EMBASE, and the Cochrane library through December 2008, restricted to randomized clinical trials, published in English	5 RCTs	Trials reporting the between-group difference in mean HbA1c during the trial was at least 0.5%, planned duration of treatment of at least 3 years, CV outcomes.
Ray, 2009[122] *Good*	To assess the effect of an intensive glucose-lowering regimen on mortality and CV outcomes	MEDLINE, the Cochrane Library, and EMBASE through January 2009	5 RCTs	Trials of intensive vs standard glucose lowering reporting CV events
Intensive blood pressure control				
Bangalore, 2011[125]	To evaluate target BP goals for patients with type 2 diabetes, impaired fasting glucose or glucose intolerance	PUBMED, EMBASE, Cochrane, through October 2010	13 RCTs	Trials with achieved SBP ≤140 mm Hg in both groups with at least 3 mm Hg difference between groups

Appendix B6. Study Characteristics of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year	Purpose of Study	Databases Searched, Date of Last Search	Number of Studies	Types of Studies Included
Reboldi, 2011[134]	To define the relation between the magnitude of BP reduction and the risk of stroke and MI in patients with diabetes	MEDLINE, EMBASE, Cochrane through March 2010	5 RCTs	Trials of more versus less intensive BP control, though criteria for inclusion not clearly defined
Aspirin				
De Berardis, 2009[132]	To assess the benefits and harms of low-dose aspiring in people with DM but without CVD	MEDLINE, Cochrane through November 2008	6 RCTs	Trials (blinded or open) of aspirin vs no aspirin reporting mortality, nonfatal MI or nonfatal stroke
Stavrakis, 2011[133]	To assess the effect of low-dose aspirin for primary prevention of CV events in people with diabetes	MEDLINE, EMBASE through November 2009	7 RCTs	Trials (blinded or open) conducted in people with no prior CVD reporting mortality, MI or stroke

Author, Year	Methods for Rating Methodological Quality of Primary Studies	Methods for Synthesizing Results of Primary Studies	Interventions
Intensive glucose control			
Buehler, 2013[114] *Good*	Assessment of allocation concealment, blinding of study participants, outcome assessors and investigators, intention to treat analysis and completeness of followup.	Random effects meta-analysis, included assessment of heterogeneity	A. Intensive glucose control (n=14,792) B. Standard glucose control (n=12,862)
Hemmingsen, 2012[115] *Good*	Assessment of sequence generation, allocation concealment, blinding or participants and study personnel, presence of incomplete outcome data, selective outcome reporting and other sources of bias.	Cochrane Handbook for Systematic Reviews methods; heterogeneity examined by meta-regression; Sensitivity analysis performed.	A. Intensive glucose control (n=16,106) B. Standard glucose control (n=13,880)
Coca, 2012[116] *Good*	Assessment of method of allocation and concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.	Forest plots were created to determine pooled measures using random effects model, heterogeneity was assessed.	A. Intensive glucose control (n=13,644) B. Standard glucose control (n=12,383)
Hemmingsen, 2011[117]	Assessment of sequence generation, allocation concealment and blinding.	Random and fixed effects models and heterogeneity assessed. Sensitivity analysis including trial sequential analysis.	A. Intensive glucose control (n=15 269) B. Standard glucose control (n=13 345) .
Boussageon, 2011[118] *Good*	Assessment of sequence generation, allocation concealment and blinding.	Calculation of risk ratios and 99% CIs, meta-analysis using used fixed effects model or random effects model if heterogeneity was significant. Absolute risk reductions calculated using the range risk estimates for each outcome in the control group of the three most powerful and recent trials (ACCORD, ADVANCE, and VADT) over a five year period. Sensitivity analysis was carried out according to the Jadad score.	A. Intensive glucose control (n=18,315) B. Standard glucose control (n= 16,218)
Castagno, 2011[119] *Good*	Assessment method unclear though authors state included studies were quality assessed; dual review was undertaken	Odds ratios (ORs) and 95% CIs, were calculated; heterogeneity was assessed. Egger's linear regression test was used to ascertain potential funnel plot asymmetry.	A. Intensive glucose control (n=19,562) B. Standard glucose control (n=17,667)
Wu, 2010[120] *Good*	Assessment of randomization, allocation and blinding.	Relative risk and 95% CI calculated and results pooled using a random effects model with sensitivity analyses. Publication bias was	A. Intensive glucose control (n=14,792) B. Standard glucose control (n=13,273)

Appendix B6. Study Characteristics of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year	Methods for Rating Methodological Quality of Primary Studies	Methods for Synthesizing Results of Primary Studies	Interventions
		assessed.	
Kelly, 2009[121] *Good*	Assessment of randomization, blinding, adjudication procedures for outcomes, loss to followup.	Relative risk and CIs calculated and pooled using fixed-effects and DerSimonian and Laird random effects models with assessment of heterogeneity.	A. Intensive glucose control (n=14,662) B. Standard glucose control (n=13,410)
Ma, 2009[123] *Good*	Assessment of randomization, allocation concealment, blinding, loss to followup/withdrawals, and similarity of baseline characteristics	Relative ratio and 95% CIs were calculated. Results pooled using a fixed effects or, if significant heterogeneity was present, a random effects model.	A. Intensive glucose control (n=5,544) B. Standard glucose control (n=3,984)
Mannucci, 2009[124] *Good*	Assessment using QUOROM methods	Expected and observed event rates reported. Heterogeneity was assessed. If present both random and a fixed-effects models used. Weighted mean differences in BMI at endpoint, and Mantel-Henzel Odds Ratio (MH-OR) with 95% CI for all categorical endpoints, were calculated. Meta-regression was performed.	A. Intensive glucose control (n=17,267 B. Standard glucose control (n=15,362)
Ray, 2009[122] *Good*	Assessment method not reported	Meta-analysis using random effects model, heterogeneity was assessed. a sensitivity analysis, odds ratios from the main analysis were compared with corresponding rate ratios. All p-values are two-sided (p<0·05).	A. Intensive glucose control (n=17,267) B. Standard glucose control (n=15,773)
Intensive blood pressure control			
Bangalore, 2011[125]	Cochrane Collaboration methods: sequence generation of allocation, allocation concealment, blinding of participants/personnel/outcomes assessors, incomplete outcome data, selective outcome reporting, and other sources of bias	Meta-regression analysis to evaluate SBP and outcomes. Sensitivity analyses used Bayesian random-effects model	A. Intensive BP lowering (achieved SBP ≤135 mm Hg; n=19,042) B. Standard BP lowering (achieved BP ≤140 mm Hg; n=18,694)
Reboldi, 2011[134]	Cochrane Collaboration methods: sequence generation of allocation, allocation concealment, blinding of participants/personnel/outcomes assessors, incomplete outcome data, selective outcome reporting, and other sources of bias	Fixed-effect and random-effect meta-regression	A. Intensive BP lowering (no specific BP targets; n=4,093) B. Standard BP lowering (no specific BP targets; n=4,239)
Aspirin			
De Berardis, 2009[132]	Assessment of allocation concealment, blinding, intention to treat and completeness of followup	Random effects meta-analysis, included assessment of heterogeneity	A. Aspirin (n=5,064) B. No aspirin (n=5,053)
Stavrakis, 2011[133]	Assessment of method of randomization, blinding and withdrawals/dropouts	Random and fixed effects models using DerSimonian-Laird method; included assessment of heterogeneity	A. Aspirin (n=not reported) B. No aspirin (n=not reported)

Abbreviations: CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; RCT = randomized, controlled trial.

Appendix B7. Results of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year *Quality*	Number of Studies	All-Cause Mortality	Cardiovascular Mortality	Myocardial Infarction	Macrovascular Events	Microvascular Events	Cardiovascular Events
Intensive vs standard control ***Number of studies; RR, 95% CI; I^2(if reported)***							
Glucose control							
Buehler, 2013[114] *Good*	8 RCTs	6 studies; 1.03, 0.90 to 1.17; I^2=50%	6 studies; 1.04, 0.83 to 1.29; I^2=60%	**Nonfatal MI: 5 studies** **0.85, 0.76 to 0.95;** **I^2=0%**			
Hemmingsen, 2012[115] *Good*	18 RCTs	18 studies; 1.01, 0.9 to 1.13; I^2=40%	18 studies; 1.06, 0.9 to 1.26; I^2=37%	Nonfatal MI: 12 studies; 0.87, 0.76 to 1.00; I^2=28%	10 studies; 0.92, 0.80 to 1.05; I^2=61%	**4 studies;** **0.89, 0.83 to 0.95;** **I^2=17%[a]**	
Coca, 2012[116] *Good*	7 RCTs						
Boussageon, 2011[118] *Good*	13 RCTs	9 studies; 1.04, 0.91 to 1.19; I^2=42%	10 studies; 1.11, 0.86 to 1.43; I^2=61%	**Nonfatal MI: 8 studies;** **0.85, 0.74 to 0.96;** **I^2=0%** Fatal or nonfatal MI: 8 studies; 0.90, 0.81 to 1.01; I^2=0%			
Castagno, 2011[119] *Good*	8 RCTs						
Hemmingsen, 2011[117] *Good*	14 RCTs	12 studies; 1.02, 0.91 to 1.13; I^2=30%	12 studies; 1.11, 0.92 to 1.35; I^2=46%	**Nonfatal MI: 8 studies;** **0.85, 0.76 to 0.95;** **I^2=0%**		**3 studies; 0.88, 0.79 to 0.97;** **I^2=45%[b]**	
Wu, 2010[120] *Good*	6 RCTs	6 studies; 0.95, 0.80 to 1.12	5 studies; 1.10, 0.79 to 1.53		6 studies; 0.92, 0.87 to 0.98; I^2=0%[c]		
Kelly, 2009[121] *Good*	5 RCTs	5 studies; 0.98, 0.84 to 1.15; I^2=72%	5 studies; 0.97, 0.76 to 1.24; I^2=76%	**Nonfatal MI** **5 studies; 0.84, 0.75 to 0.94** Fatal MI 5 studies; 0.94. -0.75 to 1.18			
Ma, 2009[123] *Good*	8 RCTs	3 studies; 1.02, 0.98 to 1.07			3 studies; 0.96, 0.92 to 1.02; I^2=0%[d]		
Mannucci, 2009[124] *Good*	5 RCTs	5 studies; OR 1.01, 0.88 to 1.15	5 studies; OR 1.01, 0.82 to 1.26	**Fatal or nonfatal MI** **5 studies;** **OR 0.85, 0.78 to 0.93**			**5 studies;** **OR 0.89, 0.83 to 0.96[e]**
Ray, 2009[122] *Good*	5 RCTs	5 studies; OR 1.02, 0.87 to 1.19	5 studies; OR 1.01, 0.82 to 1.26	**Nonfatal MI** **5 studies;** **OR 0.83, 0.75 to 0.93**			

Appendix B7. Results of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year *Quality*	Number of Studies	All-Cause Mortality	Cardiovascular Mortality	Myocardial Infarction	Macrovascular Events	Microvascular Events	Cardiovascular Events
Blood pressure control							
Bangalore, 2011[125]		**12 studies; 0.90, 0.82 to 0.98; I^2=0%** Results stratified according to achieved SBP: **SBP ≤135 mm Hg, 6 studies; 0.87, 0.79 to 0.95; I^2=0%** SBP ≤130 mm Hg, 6 studies; 1.04, 0.86 to 1.25; I^2=0%	7 studies; 0.93, 0.82 to 1.06; I^2=7% Results stratified according to achieved SBP: SBP ≤135 mm Hg, 4 studies; 0.90, 0.78 to 1.03; I^2=29% SBP ≤130 mm Hg, 3 studies; 1.11, 0.82 to 1.52; I^2=0%	8 studies; 0.92, 0.80 to 1.06; I2=0% Results stratified according to achieved SBP: SBP ≤135 mm Hg, 4 studies; 0.92, 0.76 to 1.11; I^2=13% SBP ≤130 mm Hg, 4 studies; 0.92, 0.80 to 1.06; I^2=0%			
Reboldi, 2011[134]				**5 studies; 0.87, 0.74 to 1.02; I^2=0%**			
Aspirin							
De Berardis, 2009[132]	6 RCTs	4 studies; 0.93, 0.82 to 1.05; I^2=0%	4 studies; 0.94, 0.72 to 1.23; I^2=57%	6 studies; 0.86, 0.61 to 1.21; I^2=62%			5 studies; 0.90, 0.81 to 1.0; I^2=0%
Stavrakis, 2011[133]	7 RCTs	4 studies; HR 0.99, 0.82 to 1.20; 1^2=0%	4 studies; HR 0.99, 0.62 to 1.60; I^2=39%	Fatal or nonfatal MI 3 studies; HR 0.83, 0.40 to 1.72; I^2=64%			3 studies; HR 0.89, 0.70 to 1.13; I^2=0%[f]

Appendix B7. Results of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year *Quality*	Heart Failure	Stroke	Renal Disease	Amputation	Retinopathy	Neuropathy	Harms
Intensive vs standard control ***Number of studies; RR, 95% CI; I^2 (if reported)***							
Glucose control							
Buehler, 2013[114] *Good*		Nonfatal stroke: 5 studies; 1.02, 0.88 to 1.17; I^2=0%	Nephropathy: 3 studies; 0.69, 0.42 to 1.14; I^2=73%	3 studies; 0.69, 0.44 to 1.08; I^2=0%	3 studies; 0.75, 0.37 to 1.53; I^2=65%	Autonomic: 2 studies; 1.15, 0.72 to 1.86; I^2=75% **Peripheral: 3 studies;** **0.94, 0.89 to 0.99; I^2=2%**	**Severe hypoglycemia** **5 studies;** **2.39, 1.79 to 3.18; I^2=62%**
Hemmingsen, 2012[115] *Good*	9 studies; 0.99, 0.88 to 1.12; I^2=0%	Nonfatal stroke: 11 studies; 0.96, 0.80 to 1.16; 1^2=20%	End-stage renal disease: 7 studies; 0.87, 0.71 to 1.06; I^2=0%	**8 studies;** **0.64 to 0.95;** **I^2=0%**	**8 studies;** **0.79, 0.68 to 0.92; I^2=53%**	**9 studies;** **0.78, 0.61 to 0.99; I^2=77%**	**Severe hypoglycemia** **12 studies;** **1.76, 1.46 to 2.13; I^2=95%**
Coca, 2012[116] *Good*			End-stage renal disease: 5 studies; 0.69, 0.46 to 1.05; I^2=43% Renal disease mortality: 3 studies; 0.99, 0.55 to 1.79; I^2=0%				
Boussageon, 2011[118] *Good*	9 studies; 1.17, 0.91 to 1.50; I^2=59%	Fatal or nonfatal stroke: 8 studies; 0.96, 0.83 to 1.13; I^2=0%			8 studies; 0.85, 0.71 to 1.03; I^2=54%	6 studies; 0.99, CI 0.95 to 1.03	
Castagno, 2011[119] *Good*	7 studies; 1.20, 0.96 to 1.48; I^2=69%						
Hemmingsen, 2011[117] *Good*			Nephropathy: 8 studies; 0.83, 0.64 to 1.06; I^2=75%		**7 studies;** **0.80, 0.67 to 0.94; I^2=59%**		**Severe hypoglycemia** **9 studies;** **2.39, 1.71 to 3.34; I^2=73%**
Wu, 2010[120] *Good*							
Kelly, 2009[121] *Good*	5 studies; 1.01, 0.89 to 1.14; I^2=0%	Fatal or nonfatal stroke 5 studies; 0.98, 0.86 to 1.11 Nonfatal stroke 5 studies; 0.98, 0.82 to 1.17 Fatal stroke 5 studies; 0.87, 0.63 to 1.20					**Severe hypoglycemia** **5 studies;** **2.03, 1.46 to 2.81; I^2=85%**

Appendix B7. Results of Systematic Reviews of Intensive Glucose, Blood Pressure Control, or Aspirin Use

Author, Year *Quality*	Heart Failure	Stroke	Renal Disease	Amputation	Retinopathy	Neuropathy	Harms
Ma, 2009[123] *Good*		3 studies; 0.97, 0.84 to 1.12	Nephropathy: 2 studies; 1.06, 0.75 to 1.51		2 studies; 1.01, 0.98 to 1.04	2 studies; 1.02, 0.98 to 1.07	**Severe hypoglycemia** **2 studies;** **2.34, 1.64 to 3.35; I^2=89%**
Mannucci, 2009[124] *Good*	5 studies; OR 1.01, 0.91 to 1.32	Fatal or nonfatal stroke 5 studies; OR 0.94, 0.83 to 1.06					
Ray, 2009[122] *Good*		Fatal or nonfatal stroke 5 studies; OR 0.93, 0.81 to 1.06					
Blood pressure control							
Bangalore, 2011[125]	6 studies; 0.90, 0.75 to 1.06; I^2=48% Results stratified according to achieved SBP: SBP ≤135 mm Hg, 3 studies; 0.82, 0.66 to 1.02; I^2=45% SBP ≤130 mm Hg, 3 studies; 1.03, 0.78 to 1.35; I^2=54%	**9 studies;** **0.83, 0.73 to 0.95;** **I^2=27%** Results stratified according to achieved SBP: SBP ≤135 mm Hg, 5 studies; 0.90, 0.78 to 1.03; I^2=0% **SBP ≤130 mm Hg, 4 studies;** **0.53, 0.38 to 0.75;** **I^2=0%**	**Nephropathy: 5 studies; 0.73, 0.64 to 0.84; I^2=61%** Results stratified according to achieved SBP: SBP ≤135 mm Hg, 3 studies; 0.83, 0.68 to 1.00; I^2=0% **SBP ≤130 mm Hg, 2 studies;** **0.64, 0.53 to 0.78;** **I^2=83%**				
Reboldi, 2011[134]		**5 studies;** **0.61, 0.48 to 0.79;** **I^2=0%**					
Aspirin							
De Berardis, 2009[132]		5 studies; 0.83, 0.60 to 1.14; I^2=53%					
Stavrakis, 2011[133]		Fatal or nonfatal stroke 3 studies; 0.70, 0.44 to 1.11; I^2=70%					Major bleeding (2 studies); 3.02, 0.48 to 19; I^2=66% GI bleeding (3 studies); 2.12, 0.63 to 7.08; I^2=72%

[a]Nephropathy, retinopathy, retinal photocoagulation.
[b]Nephropathy, end stage renal disease, retinopathy, retinal photocoagulation.
[c]Nonfatal MI, nonfatal stroke, CV mortality.
[d]Cardiac events, stroke, peripheral vascular disease.
[e]Fatal or nonfatal MI, stroke, peripheral artery disease.
[f]Cardiovascular mortality, fatal and nonfatal MI, nonfatal stroke.

Abbreviations: CI = confidence interval; HR, hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SBP = systolic blood pressure.

Appendix B8. Quality Assessment of Systematic Reviews of More Versus Less Intensive Treatment

Study, Year	A priori design provided?	Duplicate study selection (a) and data extraction (b)?	Comprehensive literature search performed?	Status of publication used as an inclusion criteria?	List of studies (included and excluded) provided?	Characteristics of the included studies provided?
Bangalore, 2011[125]	Yes	a. Yes b. Yes	Yes	Unclear	Included: Yes Excluded: Partial	Yes
Buehler, 2013[114]	Yes	a. Yes b. Yes	Yes	Unclear	Included: Yes Excluded: Partial	Yes
Boussageon, 2011[118]	Yes	a. Yes b. Yes	Yes	Unclear	Yes	Yes
Castagno, 2011[119]	Yes	a. Yes b. Yes	Yes	No	Yes	Yes
Coca, 2012[116]	Yes	a. Yes b. Yes	Yes	Unclear	Included: Yes; Excluded: No	Yes
De Berardis, 2009[132]	Yes	a. Yes b. Yes	Yes	No	Yes	Yes
Hemmingsen, 2011[117]	Yes	a. Yes b. Yes	Yes	No	Yes	Yes
Hemmingsen, 2012[115]	Yes	a. Yes b. Yes	Yes	No	Yes	Yes
Kelly, 2009[121]	Yes	A. Yes b. Unclear	Yes	Yes	Yes	Yes
Ma, 2009[123]	Yes	a. Yes b. Yes	Yes	Unclear	Included: Yes; Excluded: No	Yes
Mannucci, 2009[124]	Yes	a. Unclear b. Yes	Yes	Unclear	Yes	Yes
Ray, 2009[122]	Yes	a. Unclear b. Yes	Yes	No	Yes	Yes
Reboldi, 2011[134]	Yes	a. Unclear b. Yes	Yes	Yes	Included: Yes; Excluded: No	Yes
Stavrakis, 2011[133]	Yes	a. Unclear b. Yes	Yes	Unclear	Yes	Yes
Wu, 2010[120]	Yes	a. Yes b. Yes	Yes	Unclear	Yes	Yes

Appendix B8. Quality Assessment of Systematic Reviews of More Versus Less Intensive Treatment

Study, Year	Scientific quality of included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to synthesize the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest stated for systematic reviews (a) or individual studies (b)?	Quality Rating
Bangalore, 2011[125]	Yes	Yes	Yes	Yes	a. Yes b. Yes	Good
Buehler, 2013[114]	Yes	Yes	Yes	No	a. Yes b. No	Good
Boussageon, 2011[118]	Yes	Yes	Yes	No	a. Yes b. No	Good
Castagno, 2011[119]	Yes	Unclear	Yes	Yes	a. Yes b. No	Good
Coca, 2012[116]	Yes	Yes	Yes	Yes	a. Yes b. No	Good
De Berardis, 2009[132]	Yes	Yes	Yes	No	a. Yes b. No	Good
Hemmingsen, 2011[117]	Yes	Yes	Yes	Yes	a. Yes b. Yes	Good
Hemmingsen, 2012[115]	Yes	Yes	Yes	Yes	a. Yes b. Yes	Good
Kelly, 2009[121]	Yes	No	Yes	No	a. Yes b. No	Good
Ma, 2009[123]	Yes	Unclear	Yes	No	a. No b. No	Good
Mannucci, 2009[124]	Yes	yes	Yes	Yes	a. No b. No	Good
Ray, 2009[122]	Unclear	Unclear	Yes	Yes	a. Yes b. No	Good
Reboldi, 2011[134]	Yes	No	Yes	Yes	a. Yes b. No	Good
Stavrakis, 2011[133]	Yes	Unclear	Yes	No	a. Yes b. No	Good
Wu, 2010[120]	Yes	Unclear	Yes	Yes	a. No b. No	Good

Appendix B9. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Screen-Detected DM

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed	Outcomes Assessed
ADDITION								
Griffin, 2011[68]; Simmons 2012[69]; van der Donk 2013[138] ADDITION-Europe	RCT	343 general practices Denmark, UK, the Netherlands	Mean followup: 5.3 years	A. Intensive multifactorial treatment (n=1678) Glucose target: HbA1c ≤7.0% BMI target: ≤27 kg/m^2 Blood pressure target: ≤135/85 mm Hg Cholesterol target: ≤5.0 mmol/L in patients with no history of CVD; ≤4.5 mmol/L in patients with history of CVD Lifestyle education B. Routine care (n=1379) Standard level of care according to each center's recommendations	**A vs B** Mean age 60 vs 60 years 41% vs 43% female 96% vs 93% white (other races/ ethnicities not reported) Duration of diabetes: N/A; screen-detected HbA1c 6.5 v 6.6% SBP 149 vs 150 mmHg DBP 86 vs 87 mmHg TC 5.5 vs 5.6 mmol/L BMI 31.6 vs 31.6 kg/m^2 7% vs 6% history of MI 28% vs 27% smoker	Newly diagnosed type 2 diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant diisease with a poor prognosis, pregnancy or lactation	Screened: N/A Eligible: N/A Enrolled: 3057 Analyzed: 3055	Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke, revascularization, nontraumatic amputation)
Charles, 2011[135] ADDITION-Denmark	RCT	190 general practices Denmark	Duration: 5 years Mean followup: 6 years	A. Intensive multifactorial treatment (n=702) Glucose target: HbA1c ≤7.0% BMI target: ≤27 kg/m^2 Blood pressure target: ≤120/80 mmHg Cholesterol target: ≤5.0 mmol/L in patients with no history of CVD; ≤4.5 mmol/L in patients with history of CVD Lifestyle education B. Routine care (n=459) Standard level of care in Denmark	**A vs B** Mean age 60 vs 60 years 41% vs 40% female Race not reported Duration of diabetes: N/A; screen-detected SBP 149.8 vs 147.0 mmHg DBP 88.3 vs 87.3 mmHg Weight (men) 93.7 vs 94.2 kg Weight (women) 82.8 vs 84.6 kg BMI (men) 30.4 vs 30.4 BMI (women) 31.2 vs 31.5 HDL 1.4 vs 1.4 mmol/L TC 5.8 vs 5.6 mmol/L	Newly diagnosed type 2 diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant disease with a poor prognosis, pregnancy or lactation	Screened: 1,533 Eligible: 1,278 Enrolled: 1,161 Analyzed: Varied by outcome	Neuropathy

Appendix B9. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Screen-Detected DM

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed	Outcomes Assessed
van den Donk, 2010[136]; Janssen, 2009[137] ADDITION-Netherlands	RCT	79 general practices The Netherlands	Mean duration: 4.7 years (for certain outcomes)	A. Intensive multifactorial treatment: Glucose target: HbA1c <7.0% Blood pressure target: ≤120/80 mm Hg Cholesterol target: <5.0 mmol/L or <4.5 mmol/L in patients with known history of CVD+ lifestyle education (n=255) B. Routine care: Glucose target: HbA1c <8.5% Blood pressure target: <150/85 mmHg Cholesterol target: Any participant with CVD risk >25% within 10 years; patients with known CVD <5.0 mmol/L (n=243)	**A vs B** Mean age 60 vs 60 years 44% vs 48% female 99% vs 98% white Duration of diabetes: N/A; screen-detected SBP 163 vs 166 mmHg DBP 89 vs 90 mmHg HDL 1.1 vs 1.1 mmol/L TC 5.6 vs 5.6 mmol/L BMI 30.4 vs 31.2 kg/m^2	Screen-detected diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant diisease with a poor prognosis	Screened: NR Eligible: 586 Enrolled: 498 Analyzed: 498	Quality of life - Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; scale 0-100, higher score = better QoL) European Quality of Life-5 Dimensions (EQ5D; scale -0.5 to 1; higher score = better QoL) Diabetes Treatment Satisfaction Questionnaire (DTSQ; scale 0-36; higher score = greater treatment satisfaction) Problem Areas in Diabetes scale (PAID; scale 0-100; higher score = more emotional distress, lower QoL)

Appendix B9. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Screen-Detected DM

Author Year Study Name	Treatment: Mean Baseline and Achieved Values	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
ADDITION					
Griffin, 2011[68]; Simmons 2012[69], van der Donk 2013[138] ADDITION - Europe	**A vs B** HbA1c - Baseline: 7.0% vs 7.0% Achieved: 6.6% vs 6.7% Blood pressure - Baseline: 149/86 vs 150/87 mmHg Achieved: 135/80 vs 138/81 mmHg Total cholesterol - Baseline: 5.5 vs 5.6 mmol/L Achieved: 4.2 vs 4.4 mmol/L BMI - Baseline: 31.6 vs 31.6 kg/m^2 Achieved: 31.1 vs 31.0 kg/m^2	**A vs B** First CV event: 121/1678 (7%) vs 117/1377 (8%); RR 0.85 (95% CI 0.67 to 1.08); HR 0.83 (95% CI 0.65 to 1.05) All-cause mortality: 104/1678 (6%) vs 92/1377 (7%); RR 0.93 (95% CI 0.71 to 1.22); HR 0.91 (95% CI 0.69 to 1.21) CV mortality: 26/1678 (2%) vs 22/1377 (2%); RR 0.97 (95% CI 0.55 to 1.70); HR 0.88 (95% CI 0.51 to 1.51) MI: 29/1678 (2%) vs 32/1377 (2%); RR 0.74 (95% CI 0.45 to 1.22); HR 0.70 (95% CI 0.41 to 1.21) Stroke: 22/1678(1%) vs 19/1377 (1%); RR 0.95 (95% CI 0.52 to 1.74); HR 0.98 (95% CI 0.57 to 1.71) Revascularization: 44/1678 (3%) vs 44/1377 (3%); RR 0.82 (95% CI 0.54 to 1.24); HR 0.79 (95% CI 0.53 to 1.18) A vs B; stratified by country (n/N not reported): CV events - -Denmark: HR 0.83 (95% CI 0.59 to 1.16) -UK: HR 0.80 (95% CI 0.55 to 1.17) -The Netherlands: HR 0.96 (95% CI 0.45 to 2.03) All-cause mortality - -Denmark: HR 1.15 (95% CI 0.80 to 1.66) -UK: HR 0.59 (95% CI 0.35 to 0.98) -The Netherlands: HR 0.85 (95% CI 0.35 to 2.06) CV mortality - -Denmark: HR 1.46 (95% CI 0.69 to 3.12) -UK: HR 0.45 (95% CI 0.19 to 1.06) -The Netherlands: HR 0.97 (95% CI 0.14 to 6.82) MI - -Denmark: HR 0.55 (95% CI 0.28 to 1.09) -UK: HR 1.09 (95% CI 0.40 to 2.94) -The Netherlands: HR 0.95 (95% CI 0.14 to 6.52) Stroke - -Denmark: HR 0.84 (95% CI 0.34 to 2.04) -UK: HR 1.11 (95% CI 0.52 to 2.35) -The Netherlands: HR 0.95 (95% CI 0.14 to 6.56) Revascularization - -Denmark: HR 0.81 (95% CI 0.49 to 1.35) -UK: HR 0.68 (95% CI 0.32 to 1.46) -The Netherlands: HR 0.95 (95% CI 0.30 to 3.00)	None reported	Fair	Novo Nordisk; GlaxoSmithKline; Pfizer
Griffin, 2011[68]; Simmons 2012[69], van der Donk 2013[138]		Second CV event - CVD mortality: 5/1678 (0.3%) vs 3/1377 (0.2%); RR 0.82 (95% CI 0.54 to 1.24) MI: 0/1678 (0%) vs 5/1377 (0.3%); RR 0.07 (95% CI 0.004 to 1.35) Stroke: 1/1678 (0.06%) vs 1/1377 (0.07%); RR 0.82 (95% CI 0.05 to 13) Revascularization: 27/1678 (2%) vs 28/1377 (2%); RR 0.79 (95% CI 0.47	None reported	Fair	Not reported

Appendix B9. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Screen-Detected DM

Author Year Study Name	Treatment: Mean Baseline and Achieved Values	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
ADDITION - Europe (cont.)		to 1.34) Amputation: 0/1678 (0%) vs 1/1377 (0.07%); RR 0.27 (95% CI 0.01 to 6.72) Pooled risk second event: HR 0.70 (95% CI 0.43 to 1.12) Third CV event - CVD mortality: 1/1678 (0.05%) vs 3/1377 (0.2%); RR 0.27 (95% CI 0.03 to 2.63) MI: 0/1678 (0%) vs 3/1377 (0.2%); RR 0.12 (95% CI 0.006 to 2.27) Stroke: 2/1678 (0.01%) vs 0/1377 (0%); RR 4.10 (95% CI 0.20 to 85) Revascularization: 4/1678 (0.2%) vs 11/1377 (0.8%); RR 0.30 (95% CI 0.10 to 0.94) Amputation: 1/1678 (0.05%) vs 0/1377 (0%); RR 2.46 (95% CI 0.10 to 60) Pooled risk third event: HR 0.30 (95% CI 0.10 to 0.97) Pooled risk any event: HR 0.77 (95% CI 0.58 to 1.02) *Individual outcome RRs calculated; pooled HRs reported in text* Quality of life measures - A (n=1,574) vs B (n=1,287), mean between-group difference at followup SF-36 mental component score (scale 0 to 100): -0.01 (95% CI -0.03 to 0.02) SF-36 physical component score (scale 0 to 100): -0.01 (95% CI -1.2 to 1.0) Euroquel Visual Analog Scale score (scale 0 to 100): -1.17 (95% CI -4.2 to 1.9) Euroquel 5 Dimensions score (scale -0.6 to 1.0): -0.01 (95% CI -0.03 to 0.02) Well-Being Questionnaire - General score (scale 0 to 36): -0.32 (95% CI -1.31 to 0.66) Well-Being Questionnaire - Negative score (scale 0 to 12): 0.01 (95% CI -.025 to 0.27) Well-Being Questionnaire - Positive score (scale 0 to 12): -0.19 (95% CI -0.53 to 0.15) Well-Being Questionnaire - Energy score (scale 0 to 12): -0.04 (95% CI -0.38 to 0.31) Audit of Diabetes-Dependent Quality of Life score (scale -9 to 3): -0.04 (95% CI -0.20 to 0.13) Diabetes Treatment Satisfaction Questionnaire score (scale 0 to 36): -0.85 (95% CI -1.76 to 0.07)			

Appendix B9. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Screen-Detected DM

Author Year Study Name	Treatment: Mean Baseline and Achieved Values	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Charles, 2011[135] ADDITION - Denmark	**A vs B** HbA1c - Baseline: 6.4% vs 6.4% Achieved: No significant change in either group (data not reported) Blood pressure - Baseline: 147/87 vs 150/88 mmHg Achieved: Significant reduction in both groups (data not reported) Total cholesterol - Baseline: 5.5 vs 5.6 mmol/L Achieved: Significant reduction in both groups (data not reported) BMI - Baseline: 31.5 vs 31.2 kg/m^2 Achieved: No significant change in either group (data not reported)	**A vs B** Ankle brachial index ≤0.9%: 37/507 (7.3%) vs 30/329 (9.1%); RR 0.80 (95% CI 0.50 to 1.27) Measures of peripheral diabetic neuropathy: -Light touch 1/8: 69/387 (17.8%) vs 47/231 (20.3%); RR 0.88 (95% CI 0.63 to 1.22) -VDT >95% percentile: 53/235 (22.6%) vs 35/136 (25.7%); RR 0.88 (95% CI 0.60 to 1.27) -Light touch + VDT: 69/229 (30.1%) vs 47/135 (34.8%): RR 0.87 (95% CI 0.64 to 1.17) -MNSI Qst, cut ≥7: 57/656 (8.7%) vs 40/430 (9.3%); RR 0.93 (95% CI 0.64 to 1.37) Pain: 27/581 (4.6%) vs 18/400 (4.5%); RR 1.03 (95% CI 0.58 to 1.85)	None reported	Fair	NovoNordisk, Glaxo Smith Kline, Merck
van den Donk, 2010[136]; Janssen, 2009[137] ADDITION - Netherlands	**A vs B (at 1 year followup)** HbA1c - Baseline: 7.3% vs 7.4% Achieved: 6.5% vs 7.2% Blood pressure - Baseline: 166/90 vs 163/83 mm Hg Achieved: 133/78 vs 144/82 mm Hg Total cholesterol - Baseline: 5.6 vs 5.6 mmol/L Achieved: 4.4 vs 5.1 mmol/L	**A vs B** SF-36 at 1 year: -General health: 63.3 (SD 18.4) vs 64.4 (SD 18.1); p=0.63 -Vitality: 64.8 (SD 20.4) vs 67.1 (SD 18.4); p=0.81 -Mental health: 75.9 (SD 17.9) vs 79.0 (SD 15.6); p=0.56 -Physical functioning: 80.1 (SD 21.2) vs 78.1 (SD 23.2); p=0.22 -Role physical: 80.3 (SD 35.0) vs 81.1 (SD 33.5); p=0.93 -Bodily pain: 79.2 (SD 22.7) vs 82.2 (22.4); p=0.97 -Social functioning: 83.0 (SD 22.0) vs 85.7 (SD 19.2); p=0.37 -Role emotional: 86.2 (SD 30.9) vs 89.9 (SD 26.0); p=0.25 SF-36 at 3 years: -General health: 64.2 (SE 1.5) vs 65.8 (SE 1.5); p=0.45 -Vitality: 65.6 (SE 1.6) vs 67.7 (SE 1.6); p=0.35 -Mental health: 75.9 (SE 1.4) vs 79.7 (SE 1.2); p=0.04 -Physical functioning: 77.3 (SE 1.8) vs 79.1 (SE 1.7); p=0.46 -Role physical: 76.6 (SE 2.7) vs 83.4 (SE 2.4); p=0.06 -Bodily pain: 78.0 (SE 1.8) vs 81.1 (SE 1.6); p=0.20 -Social functioning: 83.2 (SE 1.7) vs 86.2 (SE 1.6); p=0.20 -Role emotional: 84.8 (SE 2.4) vs 87.0 (SE 2.4); p=0.52 EQ5D at 3 years: 0.81 (SE 0.02) vs 0.82 (SE 0.02); p=0.72 DTSQ at 5 years: 32.7 (SE 0.3) vs 32.7 (SE 0.3); p=1.00 PAID at 5 years: 9.8 (SE 1.0) vs 8.4 (SE 0.9); p=0.30	Serious AEs (hypoglycemic event requiring assistance): 1/255 (0.4%) vs 0/243 (0%); RR 2.86 (95% CI 0.12 to 70)	Fair	NovoNordisk, Glaxo Smith Kline, Merck

Abbreviations: ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes; BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HbA = glycated hemoglobin; HR = heart rate; QoL = quality of life; RR = relative risk; SD = standard deviation; UK = United Kingdom.

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
ACCORD							
ACCORD Study Group, 2011[128] ACCORD Study Group, 2008[127] Calles-Escandon, 2010[174]	RCT	77 centers US, Canada	Mean duration: 3.5 years	A. Intensive glucose control treatment (n=5128) Glucose target: HbA1c < 6.0% B. Standard treatment (n=5123) Glucose target: HbA1c 7.0-7.9%	**A vs B** Mean age 62 vs 62 years 39% vs 38% female 64% vs 65% White 20% vs 19% Black 7% vs 7% Hispanic Duration of diabetes: 10 vs 10 years Previous CV event: 36% vs 35% HbA1c: 8.3% vs 8.3% SBP: 136.2 vs 136.5 mmHg DBP: 74.8 vs 75.0 mmHg TC: 183.3 vs 183.3 mg/dL BMI: 32.3 vs 32.2 kg/m^2	Age 40-79 years, type 2 diabetes (HbA1c ≥7.5%), previous evidence of CVD or presence of CVD risk factors Excluded: Frequent/recent serious hypoglycemic events, unwillingness to do home glucose monitoring, BMI >45 kg/m^2, serum creatinine >1.5 mg/dL, other serious illness	Screened: NR Eligible: NR Enrolled: 10,251 Analyzed: 10,251 Withdrawals: 162 Loss to followup: 50
Schwartz, 2012[139] ACCORD - BONE	RCT	54 centers, US, Canada	Mean followup: 3.8 years	A. Intensive glucose control treatment (n=3655) Glucose target: HbA1c <6.0% B. Standard treatment (n=3632) Glucose target: HbA1c 7.0-7.9%	**A vs B** Mean age 63 vs 63 years 35% vs 34% female 70% vs 71% White 21% vs 21% Black 9% vs 9% other Duration of diabetes 10 vs 10 years HbA1c: 8.3% vs 8.3%	ACCORD patients with self-reported nonspinal fractures	Screened: NA Eligible: NR Enrolled: 7287 Analyzed: 6979 Withdrawals: NA Loss to followup: NA
ACCORD Study Group, 2010[79] ACCORD - BP	RCT	77 centers US, Canada	Mean followup: 4.7 years	A. Intensive BP lowering treatment (n=2362) Blood pressure target: SBP < 120 mm Hg B. Standard treatment (n=2371) Blood pressure target: SBP <140 mm Hg *Study participants also randomized to intensive (HbA1c <6.0%) or standard (HbA1c 7.0-7.9%) glucose targets; see ACCORD Study Group 2011and 2008*	A. vs B. Mean age 62 vs 62 years 48% vs 48% female 62% vs 60% non-Hispanic white 24% vs 25% Black 7% vs 7% Hispanic Duration of diabetes 9 vs 10 years HbA1c 8.4% vs 8.3% SBP 138.9 vs 139.4 mmHg DBP 77.5 vs 77.4 mmHg TC 194.1 vs 191.4 mg/dL BMI 32.3 vs 32.1 kg/m^2	Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with anatomical evidence of substantial atherosclerosis, albuminuria, LVH or at least two other CVD risk factors. Excluded: BMI >45, serum creatinine >1/5 mg/dL, other serious illness	Screened: NR Eligible: NR Enrolled: 4733 Analyzed: Withdrawals: unclear Loss to followup: 232/4733 (5%)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
Ismail-Beigi, 2012[140] ACCORD - BP	RCT	77 centers US, Canada	Mean followup: 4.7 years	A. Intensive BP lowering treatment (n=2362) Blood pressure target: SBP <120 mm Hg B. Standard treatment (n=2371) Blood pressure target: SBP <140 mm Hg *Study participants also randomized to intensive (HbA1c <6.0%) or standard (HbA1c 7.0-7.9%) glucose targets; see ACCORD Study Group 2011and 2008*	A. vs B. Mean age 62 vs 62 years 48% vs 48% female 62% vs 60% non-Hispanic white 24% vs 25% Black 7% vs 7% Hispanic Duration of diabetes 9 vs 10 years HbA1c 8.4% vs 8.3% SBP 138.9 vs 139.4 mmHg DBP 77.5 vs 77.4 mmHg TC 194.1 vs 191.4 mg/dL BMI 32.3 vs 32.1 kg/m^2	Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with anatomical evidence of substantial atherosclerosis, albuminuria, LVH or at least two other CVD risk factors. Excluded: BMI >45, serum creatinine >1/5 mg/dL, other serious illness	Screened: NR Eligible: NR Enrolled: 4733 Analyzed: Withdrawals: unclear Loss to followup: 232/4733 (5%)
O'Connor, 2012[141] Sullivan, 2007[142] ACCORD - BP HRQOL	RCT	Not reported US, Canada	Mean followup 4 years	A. Intensive blood pressure control B. Standard blood pressure control	Not reported	Randomly selected patients included in ACCORD Cost Effectiveness Analysis	Screened: NR Eligible: NR Enrolled: 1028 Analyzed: Unclear
ACCORD Study Group, 2010[143] ACCORD Eye	RCT	77 centers US, Canada		A. Intensive glucose control treatment (n=1429) B. Standard treatment (n=1427) C. Fenofibrate (n=806) D. Placebo (n=787) E. Intensive blood pressure control (n=647) F. Standard blood pressure control (n=616)	Mean age 62 years 61% male 70% white 30% nonwhite Duration of diabetes 10 years HbA1C: 8.2% LDL: 100.7 mg/dL HDL: 41.9 mg/dL SBP: 134.5 mm Hg DBP: 74.9 mm Hg BMI 32.4	ACCORD patients without history of proliferative diabetic retinopathy, lasar photocoagulation or vitrectomy	Screened: NR Eligible: NR Enrolled: 3537 Analyzed: 2865 Withdrawals: 65 post randomization exclusions Loss to followup: 616/3472 (18%)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
Anderson, 2011[144] ACCORD - HRQL	RCT	77 centers US, Canada; ACCORD HRQL Study included subset of all ACCORD participants		A. Intensive glucose control treatment (n=1,024) B. Standard treatment (n=1,029)	*Not stratified by treatment group* Mean age 62 years 40% female 65% non-Hispanic white 20% Black 7% Hispanic Duration of diabetes 10 years HbA1c: 8.3% SBP: 136.2 mmHg DBP: 74.5 mmHg BMI 32.4 kg/m	Randomly selected patients enrolled in ACCORD	*Subgroup analysis of full ACCORD population* Screened: NR Eligible: NR Enrolled: 2053 Analyzed: 1956 Withdrawals: unclear Loss to followup: unclear; 97/2053 (5%) enrolled patients excluded from analysis
ACCORD Study Group, 2010[129] ACCORD - Lipid	RCT	77 centers US, Canada	Mean followup: 4.7 years	A. Intensive lipid control (n=2765) Lipid target: not reported; intervention simvastatin + fenofibrate B. Standard treatment (n=2753) Lipid target: not reported; intervention simvastatin + placebo	A. vs B. Mean age 62 vs 62 years 31% vs 31% female 69% vs 68% white 14% vs 16% Black 8% vs 7% Hispanic Duration of diabetes 10 vs 9 years HbA1c 8.3% vs 8.3% SBP 133.8 vs 134.0 mm Hg DBP 73.9 vs 74.0 mm Hg TC 174.7 vs 175.7 mg/dL BMI 32.2 vs 32.2 kg/m^2	Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with evidence of subclinical CVD or two or more CVD risk factors, LDL 60-180 mg/dL, HDL <55 mg/dL, HDL <55 mg/dL for women or Blacks, HDL <50 mg/dL for all other groups. triglyceride level <750 mg/dL if not receiving lipid therapy or <400 mg/dL if receiving lipid therapy	Screened: NR Eligible: NR Enrolled: 5518 Analyzed: 5518

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
ADVANCE							
Patel 2007[80]; de Galan, 2009[145]; Poulter, 2009[126] ADVANCE	RCT	215 centers Asia, Austrailasia, Europe, North America	Mean followup 4.3 years (BP control) and 5.5 years (glucose control)	A. Intensive blood pressure control; addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set (n=5569) B. Standard blood pressure control; existing regimen with addition of placebo (n=5571) C. Intensive glucose control; target ≤6.5% HbA1c (n=5571) D. Standard glucose control (n=5569)	A vs B Mean age 66 vs 66 years 43% vs 43% female Race not reported Duration of diabetes 8 vs 8 years HbA1c 7.5% vs 7.5% History of major macrovascular disease 32% vs 32% History of major microvascular disease 10% vs 10% SBP 145 vs 145 mm Hg DBP 81 vs 81 mm Hg BMI 28 vs 28 kg/m^2	Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial	Screened: 12877 Eligible: 12483 Enrolled: 11140 Analyzed: 11140 Withdrawals: 2916/11140 (26%) Loss to followup: 15/11140 (0.1%)
Zoungas, 2009[130] ADVANCE	RCT	215 centers Asia, Austrailasia, Europe, North America	Mean followup 4.3 years	A. Intensive glucose control (A1c ≤6.5%) + intensive blood pressure control (addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set) (n=2783) B. Standard glucose control + standard blood pressure control; existing regimen with addition of placebo (n=2783)	A vs B Mean age 66 vs 66 years 33% vs 33% female Race not reported Duration of diabetes 8 vs 8 years HbA1c 7.5% vs 7.5% SBP 145.2 vs 145.3 mm Hg DBP 80.9 vs 80.5 mm Hg BMI 28.4 vs 28.3 kg/m^2	Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial	Screened: 12877 Eligible: 12483 Enrolled: 11140 Analyzed: 11140 (A vs B: 5566) Withdrawals: 2901/11140 (26%) Loss to followup: 15/11140 (0.1%)
Stefansdottir 2011[146] ADVANCE	RCT	215 centers Asia, Austrailasia, Europe, North America	Mean followup 5 years	A. Intensive glucose control; HbA1c target <6.5% (n=5571) B. Standard glucose control (n=5569)	A vs B Mean age 67 vs 67 years 43% vs 42% female Race not reported Duration of diabetes 8 vs 8 years HbA1c 7.5% vs 7.5% SBP 145.0 mm Hg vs 145.0 mm Hg DBP 80.8 mm Hg vs 80.5 mm Hg BMI 28 kg/m^2 vs 28 kg/m^2	Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial	Screened: 12877 Eligible: 12483 Enrolled: 11140 Analyzed: 11140 Withdrawals: 2901/11140 (26%) Loss to followup: 15/11140 (0.1%)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
Beulens 2009[147] ADVANCE Retinal Measurements Study	RCT	39 centers Asia, Australia, Europe, North America	Mean followup 4.1 years	A. Intensive blood pressure control; addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set B. Standard blood pressure control; existing regimen with addition of placebo	A vs B Mean age 66 vs 66 years 37% vs 40% female 49% vs 47% White 38% vs 38% Chinese 9% vs 10% South Asian Mean duration of diabetes 6 vs 6 years HbA1c 7/3% vs 7.5% SBP 1431. vs 142.3 mm Hg DBP 79.5 vs 79.2 mm Hg BMI 27.7 vs 27.7 kg/m^2	Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial, previous ophthalmological intervention or unlikely that good quality photos could be obtained due to cataract or pupils that did not adequately dilate	Screened: NR Eligible: 2863 Enrolled: 2130 Analyzed: 1241 Withdrawals: unclear Loss to followup: unclear (528/2130 had no usable baseline photograph; 361/2130 had no valid followup photograph)
JEDIT							
Araki, 2012[148] JEDIT	RCT	39 centers Japan	Study duration: 6 years (mean or median NR)	A. Intensive treatment: targeted HbA1c <6.9%, BMI <25, SBP <130 mmHg, DBP <85 mmHg, HDL-C >40 mg/dL, serum triglycerides <150 mg/dL, serum total cholesterol <180 mg/dL (n=585) B. Usual care: continued baseline treatment for diabetes, hypertension, or dyslipidemia without a specific goal (n=588)	A vs. B Mean age 72 vs. 72 years 54% vs 54% female Race not reported Duration of diabetes 17 vs. 18 years Mean BMI 24.0 vs. 24.3 kg/m^2 HbA1c 8.4% vs. 8.5%	Diabetic outpatients, aged 65-85 years, HbA1c ≥7.9%, or HbA1c ≥7.4% with at least one of the following: BMI ≥25, blood pressure ≥130/85 mmHg, serum total cholesterol ≥200 mg/dL Exclude: MI or stroke within previous 6 months, acute or serious illness, aphasia, or severe dementia	Screened: NR Eligible: NR Enrolled: 1,173 Analyzed: 1,173 Withdrawal over 6 years: 8.9% (104/1,173)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
JPAD							
Ogawa 2008;[149] Okada 2011[150] JPAD	RCT	163 centers Japan	Median follow up 4.4 years	A: Aspirin, 81 mg or 100 mg/day B: No aspirin	A. vs B. Mean age 65 vs 64 years 44% vs 47% female Race not reported	Type 2 diabetes, age 30-85 years, ability to provide informed consent Excluded: EKG changes consistent with ischemic changes, confirmed history of CAD, history of CVD including TIA, history of atherosclerotic disease, atrial fibrillation, pregnancy, use of antiplatelet or antithrombotic treatments, history of severe gastric of duodenal ulcer, severe CKD or allergy to aspirin	Screened: 2567 Eligible: 2454 Enrolled: 2539 Analyzed: 2539 Withdrawals: NR Loss to followup: 193
MEGA							
Tajima 2008;[84] Nakamura 2006[151] MEGA	RCT	924 centers Japan	Mean followup 5 years	A. Intensive lipid control with diet + pravastatin 10 mg/day; target total cholesterol ≤220 mg/dL (n=1093; 853 diabetes, 240 IFG) B. Standard lipid control with diet only (n=1117; 893 diabetes, 224 IFG)	Not stratified by treatment group - Persons with diabetes: Mean age 59 years 100% Japanese HbA1c 6.9% BMI 24.2 Persons with IFG: Mean age 58 years 100% Japanese HbA1c 5.5% BMI 24.4	Age 40-70 years with hypercholesterolemia (TC 220-270 mg/dL) with no history of CHD or stroke	Screened: NA Eligible: NA Enrolled: 2210 (subgroup of persons with diabetes or IFG) Analyzed: 2210 Withdrawals: unclear Loss to followup: unclear

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
SANDS							
Howard, 2008[152] SANDS	RCT	4 centers United States	36 months (mean or median NR)	A. Intensive treatment: SBP target ≤115 mmHg, DBP <75 mmHg, LDL-C <70 mg/dL, non-HDL-C <100 mg/dL (n=276) B. Usual care: SBP target <130 mmHg, DBP <85 mmHg, LDL-C <100 mg/dL, non-HDL-C <130 mg/dL (n=272)	A vs. B Mean age 55 vs. 57 years 66% vs 65% female 100% Native American Duration of diabetes 9.2 vs. 8.7 years HbA1c 8.2% vs. 7.9% BMI 34 vs. 33 kg/m^2	Native Americans aged ≥40 years with type 2 diabetes, LDL-C ≥100 mg/dL, and SBP >130 mmHg within the previous 12 months Exclude: New York Heart Association class III or IV heart failure, SBP >180 mmHg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome	Screened: 1,067 Eligible: NR Enrolled: 548 Analyzed: 499
STENO-2							
Gaede, 2008[153] Steno-2	RCT	Single center Denmark	Mean treatment duration: 7.8 years Mean post-treatment followup: 5.5 years Mean total followup: 13.3 years	A. Intensive multifactorial treatment: targets of <6.5% HbA1c, <175 mg/dL fasting serum total cholesterol, <150 mg/dL fasting serum triglyceride, <130 mmHg SBP, and <80 mmHg DBP. Patients received renin-angiotensin blockers and aspirin. (n=80) B. Usual care (n=80)	A vs. B Mean age 55 vs 55 years Sex not reported 100% vs. 100% White Mean BMI, men: 29.3 vs. 30.3 Mean BMI, women: 31.1 vs. 28.9 HbA1c 8.4% vs. 8.8%	White Danish patients with type 2 diabetes and persistent microalbuminuria	Screened: 315 Eligible: 160 Enrolled: 160 Analyzed: 160 A vs. B Withdrawal: 1.3% (1/80) vs. 2.5% (2/80) Loss to followup: 21.3% (17/80) vs. 16.3% (13/80)
UKPDS							
Holman 2008[155] UKPDS	RTC	23 centers United Kingdom	Initial trial mean duration 8 years Mean post-trial monitoring 8 years	A. Intensive BP control; BP target <150/85 mm Hg (n=758) B. Standard BP control ; <180/105 mm Hg(n=390)	*Not stratified by treatment group* Median age 53 years 41% female 82% white 9% Black 8% Asian 1% other History of retinopathy 21% Prior MI 18%	Newly diagnosed diabetes age 25-65 years referred by general practitioner	Screened: 1544 Eligible: 1292 Enrolled: 1148 Analyzed: 1148 Withdrawals: NA Loss to followup: NA (post-trial monitoring)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Study Design	No. of Centers, Country	Study Duration Mean Followup	Interventions	Baseline Demographics	Inclusion/Exclusion Criteria	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup
Holman 2008[155] UKPDS (cont.)	RTC	23 centers United Kingdom	Initial trial mean duration 10 years Mean post-trial monitoring 9 years	A. Intensive glucose control with sulfonyurea-insulin <6 mmol/L (n=2729) B. Intensive glucose control with metformin <6 mmol/L (n=342) C. Standard glucose control (n=1549)	*Not stratified by treatment group* Median age 53 years 59% male 82% white 9% Black 8% Asian 1% other History of retinopathy 21% Prior MI 18%	Newly diagnosed diabetes age 25-65 years referred by general practitioner	Screened: 5102 Eligible: NR Enrolled: 4209 Analyzed: 3277 Withdrawals: NA Loss to followup: NA (post-trial monitoring)
VADT							
Duckworth, 2009[156] VADT	RCT	20 centers United States	Study duration: accrual over 2.5 years and followup for 5-7.5 years Median followup: 5.6 years	A. Intensive glycemic treatment; if obese, metformin 2000 mg (if lean, glimepiride 8 mg) and rosaglitazone 8 mg; then insulin (n=892) B. Standard care; if obese, metformin 1000 mg (if lean, glimepiride 2 mg) and rosaglitazone 4 mg; then insulin 1 U/4 kg; then metformin 2000 mg or glimepiride 8 mg and rosaglitazone 8 mg; then insulin increase (n=899)	A vs. B Mean age 61 vs. 60 years 3% vs 3% female 64% vs 60% non-Hispanic White, 15% vs 17% Hispanic White 16% vs 17% non-Hispanic Black, 5% vs 5% other Duration of diabetes 12 vs 12 years Median HbA1c 9.4% vs. 9.4% Mean BMI 31.3 vs. 31.2 kg/m^2 Previous CV event 41% vs 40%	Patients with type 2 diabetes Exclude: HbA1c <7.5, CV events in the prior 6 months, advanced congestive heart failure, severe angina, life expectancy <7 years, BMI >40, serum creatinine >1.6 mg/dL, or transaminase more than 3 times normal	Screened: 17,700 Eligible: 2,231 Enrolled: 1,791 Analyzed: 1,791 A vs. B Withdrawal: 4.8% (43/892) vs. 7.5% (67/899) Loss to followup: 6.5% (58/892) vs. 6.3% (57/899)

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
ACCORD							
ACCORD Study Group, 2011[128] ACCORD Study Group, 2008[127] Calles-Escandon, 2010[174]	Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke) Secondary outcomes - Nonfatal MI Stroke (any; nonfatal) Mortality (all-cause; CV) Primary outcomes + revascularization or nonfatal heart failure Major CHD event	**A vs B** Pretransition (mean 3.7 years followup) - CV event: 380/5128 (2%) vs 414/5123 (2%); RR 0.92 (95% CI 0.80 to 1.05); HR 0.9 (95% CI 0.78 to 1.03) Nonfatal MI: 207/5128 (1%) vs 257/5123 (1%); RR 0.80 (95% CI 0.67 to 0.96); HR 0.79 (95% CI 0.66 to 0.95) Nonfatal stroke: 72/5128 (0.4%) vs 72/5123 (0.4%); RR 1.0 (95% CI 0.72 to 1.38); HR 0.99 (95% CI 0.72 to 1.38) CV mortality: 140/5128 (0.7%) vs 109/5123 (0.6%); RR 1.28 (95% CI 1.00 to 1.64); HR 1.27 (95% CI 0.99 to 1.63) All-cause mortality: 283/5128 (1%) vs 232/5123 (1%); RR 1.22 (95% CI 1.03 to 1.44); HR 1.21 (95% CI 1.02 to 1.44) Revascularization or hospitalization for CHF: 931/5128 (5%) vs 955/5123 (5%); RR 0.97 (95% CI 0.90 to 1.06); HR 0.96 (95% CI 0.88 to 1.06) Fatal or nonfatal MI or unstable angina: 439/5128 (2%) vs 490/5123 (3%); RR 0.90 (95% CI 0.79 to 1.01); HR 0.88 (95% CI 0.77 to 1.00) Fatal or nonfatal stroke: 78/5128 (0.4%) vs 80/5123 (0.4%); RR 0.97 (95% CI 0.71 to 1.33); HR 0.97 (95% CI 0.71 to 1.33) Fatal or nonfatal CHF: 189/5128 (1%) vs 158/5123 (0.8%); RR 1.20 (95% CI 0.97 to 1.47); HR 1.19 (95% CI 0.96 to 1.47) Through final endpoint (mean 4.9 years followup) - CV event: 503/5128 (2%) vs 543/5123 (2%); RR 0.93 (95% CI 0.82 to 1.04); HR 0.91 (95% CI 0.81 to	**A vs B** All-cause mortality: total risk estimate HR 1.21 (95% CI 1.02 to 1.44) Age - <65 yrs: 125/3397 (4%) vs 87/3382 (3%); HR 1.39 (95% CI 1.05 to 1.82) 65-69 yrs: 57/938 (6%) vs 46/947 (5%); HR 1.23 (95% CI 0.84 to 1.82) 70-74: 40/516 (8%) vs 38/537 (7%); HR 1.01 (95% CI 0.65 to 1.59) >75 yrs: 35/277 (13%) vs 32/257 (12%); HR 0.90 (95% CI 0.55 to 1.47) Gender - Male: 182/3145 (6%) vs 146/3154 (5%); HR 1.21 (95% CI 0.97 to 1.50) Female: 75/1983 (4%) vs 57/1969 (3%); HR 1.23 (95% CI 0.87 to 1.74 Race/ethnicity - White: 178/3194	**A vs B** Pretransition - Serious AEs - hypoglycemia requiring medical assistance: 558/5128 (11%) vs 189/5123 (4%); RR 2.95 (95% CI 2.51 to 3.46) Other serious AEs: 121/5128 (2%) vs 84/5123 (2%); RR 1.44 (95% CI 1.09 to 1.90) Through final endpoint - Serious AEs - hypoglycemia requiring medical assistance: 596/5128 (12%) vs 233/5123 (5%); RR 2.56 (95% CI 2.21 to 2.96) Other serious AEs: 133/5128 (3%) vs 105/5123 (2%); RR 1.27 (95% CI 0.98 to 1.63)	Good	NHLBI; numerous pharmaceutical companies (Abbott, Amylin, AstraZeneca, Bayer, Closer, GlaxoSmithKline, King, Merck, Novartis, Novo Nordisk, Omron, Sanofi-Aventis, Takeda)	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		1.03) Nonfatal MI: 287/5128 (1%) vs 344/5123 (1%); RR 0.83 (95% CI 0.72 to 0.97); HR 0.82 (95% CI 0.70 to 0.96) Nonfatal stroke: 82/5128 (0.3%) vs 94/5123 (0.4%); RR 0.83 (95% CI 0.62 to 1.11); HR 0.87 (95% CI 0.65 to 1.17) CV mortality: 187/5128 (0.7%) vs 144/5123 (0.6%); RR 1.30 (95% CI 1.05 to 1.60); HR 1.29 (95% CI 1.04 to 1.60) All-cause mortality: 391/5128 (1%) vs 327/5123 (2%); RR 1.19 (95% CI 1.04 to 1.38); HR 1.19 (95% CI 1.03 to 1.38) Revascularization or hospitalization for CHF: 1159/5128 (5%) vs 1229/5123 (6%); RR 0.94 (95% CI 0.88 to 1.01); HR 0.93 (95% CI 0.86 to 1.01) Fatal or nonfatal MI or unstable angina: 580/5128 (2%) vs 627/5123 (3%); RR 0.92 (95% CI 0.83 to 1.03); HR 0.90 (95% CI 0.81 to 1.01) Fatal or nonfatal stroke: 91/5128 (0.4%) vs 106/5123 (0.4%); RR 0.86 (95% CI 0.65 to 1.13); HR 0.86 (95% CI 0.65 to 1.13) Fatal or nonfatal CHF: 232/5128 (1%) vs 212/5123 (0.8%); RR 1.09 (95% CI 0.91 to 1.31); HR 1.09 (95% CI 0.91 to 1.32)	(6%) vs 141/3199 (4%); HR 1.21 (95% CI 0.98 to 1.52) Black: 52/996 (5%) vs 29/956 (3%); HR 1.60 (95% CI 1.01 to 2.52) Hispanic: 10/358 (3%) vs 16/380 (4%); HR 0.60 (95% CI 0.27 to 1.33) Asian/other: 17/580 (3%) vs 17/588 (3%); HR 1.06 (95% CI 0.54 to 2.07)				

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
Schwartz, 2012[139] ACCORD - BONE	Fracture Falls	**A vs B** Nonspinal fracture: 198/3655 (5%) vs 189/3632 (5%); RR 1.04 (95% CI 0.86 to 1.26); HR 1.04 (95% CI 0.86 to 1.27) Hip fracture: 11/3655 (0.3%) vs 8/3632 (0.2%); RR 1.37 (95% CI 0.55 to 3.39); HR 1.35 (95% CI 0.54 to 3.35) Ankle fracture: 44/3655 (1%) vs 40/3632 (1%); RR 1.09 (95% CI 0.71 to 1.67); HR 1.09 (95% CI 0.71 to 1.68) Foot fracture: 19/3655 (0.5%) vs 26/3632 (0.7%); RR 0.73 (95% CI 0.40 to 1.30); HR 0.71 (95% CI 0.39 to 1.28) Proximal humerus fracture: 23/3655 (0.6%) vs 25/3632 (0.6%); RR 0.91 (95% CI 0.52 to 1.60); HR 0.90 (95% CI 0.51 to 1.59) Distal forearm fracture: 21/3655 (0.5%) vs 14/3632 (0.4%); RR 1.49 (95% CI 0.76 to 2.93); HR 1.5 (95% CI 0.76 to 2.95) Falls: 1122/3364 (33%) vs 1133/3418 (33%); RR 1.01 (95% CI 0.94 to 1.08); HR not reported	NR	NR	Good		

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
ACCORD Study Group, 2010[79] ACCORD - BP	Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke) Secondary outcomes - All-cause mortality CV mortality Nonfatal MI Nonfatal stroke Fatal or nonfatal congestive heart failure	**A vs B** Any CV event: 208/2363 (9%) vs 237/2371 (10%); HR* 0.88 (95% CI 0.73 to 1.06) Nonfatal MI: 126/2362 (5%) vs 146/2371 (6%); RR 0.87 (0.69 to 1.09); HR 0.87 (95% CI 0.68 to 1.10) Fatal and nonfatal stroke: 36/2363 (2%) vs 62/2371 (3%); RR 0.58 (95% CI 0.39 to 0.88); HR 0.59 (95% CI 0.39 to 0.89) Nonfatal stroke: 34/2363 (1%) vs 55/2371 (2%); HR 0.63 (95% CI 0.41 to 0.96) All-cause mortality: 150/2363 (6%) vs 144/2371 (6%); RR 1.11 (0.89 to 1.38); AHR 1.07 (95% CI 0.85 to 1.35) CV mortality: 60/2363 (3%) vs 58/2372 (2%); RR 1.04 (95% CI 0.73 to 1.48); HR 1.06 (95% CI 0.74 to 1.52) Any CV event + revascularization: 521/2363(2%) vs 551/2371 (2%); HR 0.95 (95% CI 0.84 to 1.07) Major CHD event: 253/2363 (11%) vs 270/2371 (11%); HR 0.94 (95% CI 0.79 to 1.12) Fatal or nonfatal heart failure: 83/2363 (4%) vs 90/2371 (4%); HR 0.94 (95% CI 0.70 to 1.26) **AHRs adjusted for: assignment to intensive glucose lowering arm, clinical center network, presence/absence of previous CV event*	NR	**A vs B** Serious treatment-related adverse events: 77/2362 (3%) vs 30/2371 (1%); RR 2.58 (95% CI 1.70 to 3.91) Other serious AEs (end-stage renal disease or need for dialysis): 59/2362 (2%) vs 58/2371 (2%); RR 1.02 (95% CI 0.71 to 1.46)	Good	NHLBI; numerous pharmaceutical companies (Abbott, Amylin, AstraZeneca, Bayer, Closer, GlaxoSmithKline, King, Merck, Novartis, Novo Nordisk, Omron, Sanofi-Aventis, Takeda)	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
Ismail-Beigi, 2012[140] ACCORD - BP	Primary outcome- Renal failure, retinal photocoagulation or vitrectomy (to treat retinopathy) Secondary outcomes– Nephropathy Diabetic eye complications Neuropathy	**A vs B** Primary outcome: 269/2356 (11%) vs 258/2370 (11%); HR 1.08 (95% CI 0.91 to 1.28) Nephropathy outcomes - Microalbuminuria: 306/1473 (21%) vs 375/1501 (25%); HR 0.84 (95% CI 0.72 to 0.97) Macroalbuminuria: 116/2038 (6%) vs 146/2059 (7%); HR 0.81 (95% CI 0.63 to 1.03) Renal failure: 61/2356 (3%) vs 64/2370 (3%); HR 1.00 (95% CI 0.71 to 1.43) Eye outcomes – Retinal photocoagulation or vitrectomy: 217/2262 (10%) vs 208/2282 (9%); HR 1.09 (95% CI 0.90 to 1.32) Cataract surgery: 339/2262 (15%) vs 361/2282 (16%); HR 0.98 (95% CI 0.85 to 1.14) Loss of visual acuity (3-line decrease): 819/2339 (35%) vs 849/2352 (36%); RR 0.97 (0.90 to 1.05); HR 0.98 (95% CI 0.89 to 1.08) Neuropathy outcomes – Score >2 on Michigan Neuropathy Screening Instrument: 722/1353 (53%) vs 781/1388 (56%); RR 0.95 (0.89 to 1.02); HR 0.95 (95% CI 0.86 to 1.05) Loss of vibratory sensation: 668/1569 (43%) vs 737/1582 (47%); HR 0.92 (95% CI 0.83 to 1.02) Loss of light touch: 267/2134 (13%) vs 294/2115; HR 0.91 (95% CI 0.77 to 1.08)	NR	NR	Good	NR	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
O'Connor, 2012[141] Sullivan, 2007[142] ACCORD - BP HRQOL	Quality of life - 36-Item Short Form Health Survey (SF 36) Diabetes Symptoms Distress Checklist (DSC) World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ) Patient Health Questionnaire (PHQ-9)	**A vs B** *Mean change from baseline (SE)* SF-36 physical component score: -0.8 (0.19) vs -0.2 (0.19); p=0.02 SF-36 mental component score: 0.5 (0.39) vs 0.4 (0.40); p=0.77 DSC total score: -1.4 (0.34) vs -1.1 (0.35); p=0.48 DSC symptom distress: -0.04 (0.02) vs -0.04 (0.02); p=0.98 DSC treatment satisfaction score: 13.3 (0.54) vs 13.1 (0.55); p=0.84 PHQ-9 continuous score: -1.1 (0.14) vs -0.9 (0.14); p=0.29	NR	NR	Good	NHLBI, National Institute of Diabetes and Digestive and Kidney Diseases, CDC	
ACCORD Study Group, 2010[143] ACCORD Eye	Progression of diabetic retinopathy Moderate vision loss	**A vs B** Progression of diabetic retinopathy: 104/1429 (7%) vs 149/1427 (10%); OR 0.67 (95% CI 0.51 to 0.87) *Moderate vision loss: 409/1715 (24%) vs 457/1737 (26%); OR 0.88 (95% CI 0.77 to 1.01) **C vs D** Progression of diabetic retinopathy: 52/806 (7%) vs 80/787 (10%); OR 0.60 (95% CI 0.42 to 0.87) Moderate vision loss: 227/965 (24%) vs 233/950 (25%); OR 0.95 (95% CI 0.79 to 1.14) **E vs F** Progression of diabetic retinopathy: 67/647 (10%) vs 54/616 (9%); OR 1.23 (95% CI 0.84 to 10.4) Moderate vision loss: 221/798 (28%) vs 185/748 (25%) OR 1.17 (95% CI 0.96 to 1.42) *ORs adjusted for other treatments	NR	NR	Good	NR	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
Anderson, 2011[144] ACCORD - HRQL	Quality of life - 36-Item Short Form Health Survey (SF 36) Diabetes Symptoms Distress Checklist (DSC) World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ) Patient Health Questionnaire (PHQ-9)	**A vs B** *Least squares mean, 95% CI** SF-36 physical component score: -1.1 (-2.0 to -0.2) vs -1.6 (-2.5 to -0.7); p=0.03 SF-36 mental component score: 0.8 (-1.0 to 2.6) vs 1.4 (-0.5 to 3.2); p=0.29 DSC total score: -0.4 (-1.9 to 1.0) vs 0.1 (-1.4 to 1.6); p=0.19 DSC symptom distress: -0.1 (-0.2 to 0.0) vs 0.0 (-0.1 to 0.1); p=0.15 DTSQ treatment satisfaction scale: 11.1 (8.6 to 13.5) vs 13.5 (11 to 15.9); p<0.001 DTSQ perceived hyperglycemia: -1.2 (-1.5 to -0.9) vs -1.7 (-2.0 to -1.5); p<0.0001 DTSQ perceived hypoglycemia: 0.4 (0.1 to 0.6) vs 0.8 (0.5 to 1.0); p<0.0001 PHQ-9 continuous score: -1.0 (-1.7 to -0.4) vs -0.9 (-1.5 to -0.3); p=0.44 **Analyses adjusted for the following variables: previous CVD, secondary trial, secondary trial assignment, age, race, sex, duration of diabetes, smoking, living alone, weight, waist circumference, BMI, baseline HbA1c, fasting blood glucose, SBP and DBP, heart rate, neuropathy, retinal surgery, macro- and microalbuminuria, insulin, sulfonylureas, thiazolidinedione, b-blockers, antihypertensive medication, and triglycerides*	NR	NR	Good	NR	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
ACCORD Study Group, 2010[129] ACCORD - Lipid	Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke) Secondary outcomes - Nonfatal MI Stroke (any; nonfatal) Mortality (all-cause; CV) Hospitalization or death due to heart failure Primary outcome, revascularization or nonfatal heart failure Major CHD event (fatal coronary event, nonfatal MI, unstable angina)	**A vs B** CV event: 291/2765 (11%) vs 310/2753 (11%); RR 0.93 (95% CI 0.80 to 1.09); AHR* 0.92 (95% CI 0.79 to 1.08) CV event, revascularization or hospitalization for CHF: 641/2765 (23%) vs 667/2753 (24%); RR 0.96 (95% CI 0.87 to 1.05); AHR 0.94 (95% CI 0.85 to 1.05) Major CHD event: 332/2765 (12%) vs 353/2753 (13%); RR 0.93 (95% CI 0.81 to 1.08); AHR 0.92 (95% CI 0.79 to 1.07) Nonfatal MI: 173/2765 (6%) vs 186/2753 (7%); RR 0.93 (95% CI 0.76 to 1.13); AHR 0.91 (95% CI 0.74 to 1.12) Stroke, fatal or nonfatal: 51/2765 (2%) vs 48/2753 (2%); RR 1.06 (95% CI 0.72 to 1.56); AHR 1.05 (95% CI 0.71 to 1.56) Stroke, nonfatal: 47/2765 (2%) vs 40/2753 (1%); RR 1.17 (95% CI 0.77 to 1.78); AHR 1.17 (95% CI 0.76 to 1.78) All-cause mortality: 203/2765 (7%) vs 221/2753 (8%); RR 0.91 (95% CI 0.76 to 1.10); AHR 0.91 (95% CI 0.75 to 1.10) CV mortality: 99/2765 (4%) vs 114/2753 (4%); RR 0.86 (95% CI 0.66 to 1.13); AHR 0.86 (95% CI 0.66 to 1.12) Fatal or nonfatal CHF: 120/2765 (4%) vs 143/2753 (5%); RR 0.84 (95% CI 0.66 to 1.06); AHR 0.82 (95% CI 0.65 to 1.05) **Hazard ratios adjusted for number, timing and results of interim monitoring*	**A vs B** CV event (primary outcome) -Women: 77/851 (9%) vs 56/843 (7%); RR* 1.36 (95% CI 0.98 to 1.9) Men: 214/1914 (11%) vs 254/1910 (13%); RR 0.84 (95% CI 0.71 to 0.997) Age <65 years: 149/1838 (8%) vs 173/1822 (10%); RR 0.85 (0.69 to 1.05) Age >65 years: 139/927 (15%) vs 137/931 (15%); RR 1.02 (95% CI 0.82 to 1.27) Nonwhite race: 83/856 (10%) vs 73/888 (8%); RR 1.18 (95% CI 0.87 to 1.59) White race: 208/1909 (11%) vs 237/1865 (13%); RR 0.86 (95% CI 0.72 to 1.02) **Calculated relative risks; hazard ratios and confidence intervals only reported graphically in text, no data shown.*	**A vs B** Serious adverse events: 96/2765 (3%) vs 74/2753 (3%); RR 1.29 (95% CI 0.96 to 1.74)	Good	NR	Subgroup data reported

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
ADVANCE							
Patel 2007[80]; de Galan, 2009[145]; Poulter, 2009[126] ADVANCE	Composite outcome: major macrovascular (CV mortality, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events Macrovascular events Microvascular events All-cause mortality CV mortality Major coronary events (fatal CHD, nonfatal MI) Coronary events (major coronary event, silent MI, coronary revascularization, hospital admission for unstable angina Cerebrovascular events (major cerebrovascular event, TIA, subarachnoid hemorrhage) Heart failure (death, worsening or hospitalization) Peripheral vascular disease New or worsening nephropathy New or worsening retinopathy Microalbuminuria Visual deterioration New or worsening neuropathy Cognitive function Dementia Hospitalization	**A vs B** Macro- and microvascular outcomes: 861/5569 (16%) vs 938/5571 (17%); RR 0.92 (95% CI 0.84 to 1.00); Relative Risk Reduction (RRR) 9% (95% CI 0 to 17) Macrovascular outcomes: 480/5569 (9%) vs 520/5571 (9%); RR 0.92 (95% CI 0.82 to 1.04); RRR 8% (95% CI -4 to 19) Microvascular outcomes: 439/5569 (8%) vs 477/5571 (9%); RR 0.92 (95% CI 0.81 to 1.04); RRR 9% (95% CI -4 to 20) All-cause mortality: 408/5569 (7%) vs 471/5571 (9%); RR 0.87 (95% CI 0.76 to 0.98); RRR 14% (95% CI 2 to 25) CV death: 211/5569 (4%) vs 257/5571 (5%); RR 0.82 (95% CI 0.69 to 0.98); RRR 18% (95% CI 2 to 32) Non-CV death: 197/5569 (7%) vs 212/5571 (4%); RR 0.93 (95% CI 0.77 to 1.12); RRR 8% (95% CI -12 to 24) Any coronary event: 468/5569 (8%) vs 535/5571 (10%); RR 0.84 (95% CI 0.75 to 0.95); RRR 14% (95% CI 2 to 24) Major coronary events: 265/5569 (5%) vs 294/5571 (5%); RR 0.90 (95% CI 0.77 to 1.06); RRR 11% (95% CI -6 to 24) Other coronary events: 283/5569 (5%) vs 324/5571 (6%); RR 0.87 (95% CI 0.75 to 1.02); RRR 14% (95% CI -1 to 27) Any cerebrovascular event: 286/5569 (5%) vs 303/5571 (5%); RR 0.94 (95% CI 0.81 to 1.11); RRR 6% (95% CI -10 to 20) Major cerebrovascular events: 215/5569 (4%) vs 218/5571 (4%); RR 0.99 (95% CI 0.82 to 1.19); RRR 2% (95% CI -18 to 19)	**A vs B** Any major macrovascular or microvascular event Age <65 years: 325/2256 (14%) vs 346/2276(15%); RR 0.95 (95% CI 0.82 to 1.09); RRR 6% (95% CI -10 to 19) Age >65 years: 536/3308 (16%) vs 592/3295 (18%); RR 0.90 (95% CI 0.81 to 1.00); RRR 11% (95% CI 0 to 21) Men: 546/3212 (17%) vs 594/3194 (19%); RR 0.91 (95% CI 0.82 to 1.02); RRR 10% (95% CI -5 to 23) Women: 315/2368 (13%) vs 344/2392 (15%); RR 0.93 (95% CI 0.80 to 1.07); RRR 8% (95% CI -7 to 21)	Withdrawals due to adverse events: 320/5569 (6%) vs 160/5571 (3%); RR 2.00 (95% CI 1.66 to 2.41) Serious adverse events: 67/5569 (1%) vs 66/5571 (1%); RR 1.02 (95% CI 0.72 to 1.42)	Good	Servier; National Health and Medical Research Council of Australia	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		Other cerebrovascular events: 79/5569 (1%) vs 99/5571 (2%); RR 0.80 (95% CI 0.60 to 1.07); RRR 21% (95% CI -6 to 410 Any renal event: 1243/5569 (22%) vs 1500/5571 (27%); RR 0.83 (95% CI 0.78 to 0.89); RRR 21% (95% CI 15 to 27); HR 0.79 (95% CI 0.73 to 0.85) New or worsening nephropathy: 181/5569 (3%) vs 216/5571 (4%); RR 0.84 (95% CI 0.69 to 1.02); RRR 18% (95% CI -1 to 32) New microalbuminuria: 1094/5569 (20%) vs 1317/5571 (24%); RR 0.83 (95% CI 0.77 to 0.89); RRR 21% (95% CI 14 to 27) Any eye event: 2531/5569 (45%) vs 2611/5571 (47%); RR 0.97 (95% CI 0.93 to 1.01); RRR 5% (95% CI -1 to 10) New or worsening retinopathy: 289/5569 (5%) vs 286/5571 (5%); RR 1.01 (95% CI 0.86 to 1.19); RRR -1% (95% CI -18 to 15) Visual deterioration: 2246/5569 (44%) vs 2514/5571 (45%); RR 0.89 (95% CI 0.86 to 0.93); RRR 5% (95% CI -1 to 10)					
		C vs D Macrovascular events: 1009/5571 (18%) vs 1116/5569 (20%); RR 0.90 (95% CI 0.84 to 0.98); RRR 10% (95% CI 2. to 18) Microvascular events: 526/5571 (9%) vs 605/5569 (11%); RR 0.87 (95% CI 0.78 to 0.97); RRR 14% (95% CI 3 to 23) All-cause mortality: 498/5571 (9%) vs 533/5569 (11%); RR 0.93 (95% CI 0.83 to 1.05); RRR 7% (95% CI -6 to 17) CV mortality: 253/5571 (5%) vs 289/5569 (5%); RR 0.88 (95% CI 0.74 to 1.03); RRR 12% (95% CI -4					

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		to 26) Major coronary events: 310/5571 (6%) vs 337/5569 (6%); RR 0.92 (95% CI 0.79 to 1.07); RRR 8% (95% CI -7 to 21) Nephropathy: 230/5571 (4%) vs 292/5569 (5%); RR 0.79 (95% CI 0.67 to 0.93); RRR 21% (95% CI 7 to 34)					
Zoungas, 2009[130] ADVANCE	Composite outcome: major macrovascular (CV mortality, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events Macrovascular events Microvascular events All-cause mortality CV mortality Major coronary events (fatal CHD, nonfatal MI) Cerebrovascular events (major cerebrovascular event, TIA, subarachnoid hemorrhage) Any renal event New or worsening nephropathy New or worsening retinopathy Microalbuminuria Macroalbuminuria	**A vs B** Major macrovascular and microvascular events: 431/2783 (15%) vs 498/2783 (18%); HR 0.85 (95% CI 0.75 to 0.97) Macrovascular events: 246/2783 (9%) vs 265/2783 (9%); HR 0.92 (95% CI 0.77 to 1.10) Microvascular events: 213/2783 (8%) vs 260/2783 (9%); HR 0.81 (95% CI 0.68 to 0.97) All-cause mortality: 198/2783 (7%) vs 240/2783 (9%); HR 0.82 (95% CI 0.68 to 0.99) CV mortality: 104/2783 (4%) vs 136/2783 (5%); HR 0.76 (95% CI 0.59 to 0.98) Major coronary events: 133/2783 (5%) vs 155/2783 (6%); HR 0.92 (95% CI 0.77 to 1.10) Cerebrovascular events: 111/2783 (4%) vs 107/2783 (4%); HR 1.03 (95% CI 0.79 to 1.35) Any renal event: 590/2783 (21%) vs 777/2783 (28%); HR 0.72 (95 %CI 0.65 to 0.81) New or worsening nephropathy: 81/2783 (3%) vs 120/2783 (4%); RR 0.68 (95% CI 0.51 to 0.89); HR 0.67 (95% CI 0.50 to 0.88) New or worsening retinopathy: 147/2783 (5%) vs 153/2783 (5%); HR 0.96 (95% CI 0.76 to 1.20) Microalbuminuria: 525/2783 (19%) vs 673/2783 (24%); HR 0.75 (95% CI	NR	NR	Good	Servier; National Health and Medical Research Council of Australia	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		0.67 to 0.84) Macroalbuminuria: 44/2783 (2%) vs 3% (95/2783): HR 0.46 (95% CI 0.32 to 0.65)					
Stefansdottir 2011[146] ADVANCE	Cancer	**A vs B** Cancer mortality: 41/5571 (0.7%) vs 35/5569 (0.6%); HR 1.17 (95% CI 0.96 to 1.27) Any neoplasm: 409/5571 (7%) vs 372/5569 (7%); HR 1.11 (95% CI 0.96 to 1.27) Malignant neoplasms: 363/5571 (7%) vs 337/5569 (6%); HR 1.08 (95% CI 0.93 to 1.26) Malignant neoplasms, except lymphoid, tissue: 328/5571 (6%) vs 303/5569 (5%); HR 1.09 (95% CI 0.93 to 1.27) Lip, oral cavity and pharynx: 10/5571 (0.2%) vs 7/5569 (0.1%); HR 1.43 (95% CI 0.54 to 3.75) Digestive organs: 119/5571 (2%) vs 103/5569 (2%); HR 1.16 (95% CI 0.89 to 1.51) Pancreatic cancer: 16/5571 (0.3%) vs 16/5569 (0.3%); HR 1.00 (95% CI 0.50 to 2.00) Respiratory organs: 55/5571 (1%) vs 61/5569 (1%); HR 0.90 (95% CI 0.63 to 1.30) Breast cancer: 33/5571 (0.6%) vs 31/5569 (0.6%); HR 1.07 (95% CI 0.65 to 1.74) Female genital organs: 6/5571 (0.1%) vs 10/5569 (0.2%); HR 0.60 (95% CI 0.22 to 1.65) Male genital organs: 43/5571 (0.8%) vs 43/5569 (0.8%); HR 1.00 (95% CI 0.66 to 1.53) Lymphoid, tissue: 21/5571 (0.4%) vs 19/5569 (0.3%); HR 1.10 (95% CI 0.59 to 2.05)	NR	NR	Good	NR	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
Beulens 2009[147] ADVANCE Retinal Measurements Study	ETDRS progression ≥2 steps	**A vs B** ETDRS progression ≥2 steps: 103/796 (13%) vs 84/806 (10%); adjusted OR 0.78 (95% CI 0.57 to 1.06)	NR	NR	Good	Servier; National Health and Medical Research Council of Australia	Intensive glucose outcomes included in SR ET
JEDIT							
Araki, 2012[148] JEDIT	Cardiovascular morbidity and mortality; all-cause mortality	Events and p-values of between-group comparisons (numbers for groups NR) Fatal MI: 12 events (p=0.08) Sudden death: 13 events (p=0.99) Fatal stroke: 6 events (p=0.66) Death due to renal failure: 3 events (p=0.08) Death due to hyper/hypoglycemia: 1 event (p=0.32) Nonfatal MI: 17 events (p=0.998) Coronary revascularization: 18 events (p=0.028) Hospitalization for CHF: 15 events (p=0.19) Nonfatal stroke: 63 events (p=0.28) Diabetic ulcer or gangrene: 12 events (p=0.56) Death due to diabetes: 35 events (p=0.85) Death not related to diabetes: 59 events (p=0.30) Coronary vascular events: 55 events (p=0.99) Any stroke: 67 events (p=0.29)	NR	NR	Fair	Japanese Ministry of Health, Labour, and Welfare; Japan Foundation for Aging and Health	Reduced revascularizations only; no proportions reported by group
JPAD							
Ogawa 2008;[149] Okada 2011[150] JPAD	Primary outcome - Any atherosclerotic event (sudden death, death due to coronary, cerebrovascular and aortic causes, nonfatal MI, unstable angina, exertional angina, nonfatal ischemic or hemorrhagic stroke, transient ischemic attack, nonfatal aortic or peripheral vascular	**A vs B** Primary outcome- Any atherosclerotic event: 68/1262 (5.4%) vs 8/61277 (6.7%); HR 0.80 (95% CI 0.58 to1.10) Secondary outcomes - Coronary or cerebrovascular mortality: 1/1262 (0.08%) vs 10/1277 (0.8%); HR 0.10 (95% CI 0.01 to 0.79) Fatal MI: 0/1262 (0%) vs 5/1277 (0.4%); RR 0.09 (95% CI 0.005 to	NR	**A vs B** Serious AEs (GI bleed requiring transfusion): 4/1262 (0.3%) vs 0/1277 (0%); RR 9.11 (95% CI 0.49 to 169)	Fair	Ministry of Health, Labour, and Welfare	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
	disease) Secondary outcomes - Coronary or cerebrovascular mortality Fatal MI Nonfatal MI Unstable angina Stable angina Fatal or nonfatal cerebrovascular disease Fatal stroke Nonfatal ischemic stroke Nonfatal hemorrhagic stroke Transient ischemic attack Peripheral artery disease	1.66) *HR not reported in text, RR calculated* Nonfatal MI: 12/1262 (1%) vs 9/1277 (0.7%); HR 1.34 (95% CI 0.57 to 3.19) Unstable angina: 4/1262 (0.3%) vs 10/1277 (0/8%); HR 0.40 (95% CI 0.13 to 1.29) Stable angina: 12/1262 (1%) vs 11/1277 (0.9%); HR 1.10 (95% CI 0.49 to 2.50) Fatal or nonfatal cerebrovascular disease: 28/1262 (2%) vs 32/1277 (3%); HR 0.84 (95% CI 0.53 to 1.32) Fatal stroke: 1/1262 (0.08%) vs 5/1277 (0.4%); HR 0.20 (95% CI 0.02 to 1.74) Nonfatal ischemic stroke: 22/1262 (2%) vs 24/1277 (2%); HR 0.93 (95% CI 0.52 to 1.66) Nonfatal hemorrhagic stroke: 5/1262 (0.4%) vs 3/1277 (0.2%); HR 1.68 (95% CI 0.40 to 7.04) Transient ischemic attack: 5/1262 (0.5%) vs 8/1277 (0.6%); HR 0.63 (95% CI 0.21 to 1.93) Peripheral artery disease: 7/1262 (0.6%) vs 11/1277 (0.9%); HR 0.64 (95% CI 0.25 to 1.65)					
MEGA							
Tajima 2008;[84] Nakamura 2006[151] MEGA	All-cause mortality CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization, angina) Stroke Cardiovascular disease Cerebral infarction	**A vs B (Diabetes group)*** All-cause mortality: 16/853 (2%) vs 28/893 (3%); RR 0.60 (95% CI 0.33 to 1.10); AHR 0.61 (95% CI 0.33 to 1.12) CHD: 29/853 (3%) vs 43/893 (5%); RR 0.71 (95% CI 0.45 to 1.12); AHR 0.71 (95% CI 0.44 to 1.13) Stroke: 14/853 (2%) vs 21/893 (2%); RR 0.70 (95% CI 0.36 to 1.36); AHR 0.70 (95% CI 0.36 to 1.38) CVD events: 46/853 (5%) vs 68/893 (8%); RR 0.71 (95% CI 0.49 to 1.02); AHR 0.71 (95% CI 0.49 to 1.03)	NR	NR	Fair	NR	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		Cerebral infarction: 9/853 (1%) vs 18/893 (2%); RR 0.52 (95%CI 0.24 to 1.16); AHR 0.52 (95% CI 0.23 to 1.16) **A vs B (IFG group)*** All-cause mortality: 4/240 (2%) vs 1/224 (0.4%); RR 4.07 (95% CI 0.46 to 36); AHR 4.36 (95% CI 0.49 to 39) CHD: 6/240 (3%) vs 7/224 (3%); RR 0.87 (95% CI 0.30 to 2.56); AHR 0.89 (95% CI 0.30 to 2.66) Stroke: 0/240 (0%) vs 4/224 (2%); RR 0.10 (95% CI 0.006 to 1.92); AHR not estimated CVD events: 6/240 (3%) vs 12/224 (5%); RR 0.47 (95% CI 0.18 to 1.22); AHR 0.52 (95% CI 0.20 to 1.39) Cerebral infarction: 0/240 (0%) vs 4/224 (2%); RR 0.10 (95% CI 0.006 to 1.92); AHR not estimated **A vs B (Normal glucose group - Contextual Question 2)*** All-cause mortality: 23/2773 (0.8%) vs 37/2849 (1%); RR 0.64 (95% CI 0.38 to 1.07); AHR 0.65 (95% CI 0.39 to 1.10) CHD: 22/2773 (0.8%) vs 35/2849 (1%); RR 0.65 (95% CI 0.38 to 1.10); AHR 0.65 (95% CI 0.38 to 1.11) Stroke: 24/2773 (0.9%) vs 36/2849 (1%); RR 0.68 (95% CI 0.41 to 1.15); AHR 0.70 (95% CI 0.47 to 1.17) CVD events: 50/2772 (2%) vs 73/2849 (3%); RR 0.70 (95% CI 0.49 to 1.01); AHR 0.71 (95% CI 0.50 to 1.02) Cerebral infarction: 16/2773 (0.6%) vs 23/2849 (0.8%); RR 0.71 (95% CI 0.38 to 1.35); AHR 0.73 (95% CI 0.38 to1.37)					

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
SANDS							
Howard, 2008[152] SANDS	Cardiovascular events (fatal and nonfatal CVD events, nonfatal MI, nonfatal stroke, unstable angina, revascularization)	**A vs B** Incidence of primary CV events: 11/252 (4%) vs. 8/247 (3%); RR 1.35 (95% CI 0.55 to 3.29) Incidence of other CV events: 1/252 (0.4%) vs. 3/247 (1%); RR 0.33 (95% CI 0.03 to 3.12) Non-CV death: 2/252 (0.8%) vs. 4/247 (2%); RR 0.49 (95% CI 0.09 to 2.65)	NR	A vs. B Any adverse event: 38.5% (97/252) vs. 26.7% (66/247); RR 1.44, 95% CI 1.11 to 1.87 Any serious adverse event: 26.6% (67/252) vs. 15.4% (38/247); RR 1.73, 95% CI 1.21 to 2.47	Good	National Heart, Lung, and Blood Institute; National Institutes of Health; First Horizon Pharmacy; Merck and Co; and Prizer	No benefit on clinical health outcomes; Adverse events more common in intensive group
STENO-2							
Gaede, 2008[153] Steno-2	All-cause mortality, cardiovascular morbidity and mortality, amputation, nephropathy, retinopathy, autonomic neuropathy, peripheral neuropathy	**A vs B** All-cause mortality: 24/80 (30%) vs. 40/80 (50%); ARR 20% (p=0.02); HR 0.54 (95% CI 0.32 to 0.89); RR 0.60 (95% CI 0.40 to 0.90) CV mortality: 9/80 (11%) vs. 19/80 (24%); HR 0.43 (95% CI 0.19 to 0.94); Adjusted HR 0.43 (95% CI 0.19 to 0.95); RR 0.47 (95% CI 0.23 to 0.98) Any CV event: 51 events in 25 patients vs. 158 events in 48 patients; ARR 29%, HR 0.41 (95% CI 0.25 to 0.67) MI: 8/80 (10%) vs. 21/80 (26%); RR 0.38 (95% CI 0.18 to 0.81) Stroke: 6/80 (8%) vs. 18/80 (23%); RR 0.33 (95% CI 0.14 to 0.80) Revascularization: 6/80 (8%) vs. 10/80 (13%); RR 0.60 (95% CI 0.23 to 1.57) Amputation: 6/80 (8%) vs. 14/80 (18%); RR 0.43 (95% CI 0.17 to 1.06) Nephropathy: 20/80 (25%) vs. 37/80 (46%); RR 0.44 (95% CI 0.25 to 0.77) Retinopathy: 41/80 (51%) vs. 54/80 (68%); RR 0.57 (95% CI 0.37 to 0.88) Blindness in at least one eye: 2/80	NR	A vs. B Symptomatic hypoglycemia: 80% (64/80) vs. 70% (56/80); RR 1.14, 95% CI 0.95 to 1.37 Major hypoglycemic episodes: 13% (10/80) vs. 17% (14/80); RR 0.71, 95% CI 0.34 to 1.51	Good	Danish Health Research Council	Many significant benefits; All patients counseled at the end of the treatment period about the benefits of intensive intervention

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		(3%) vs. 7/80 (9%); RR 0.51 (95% CI 0.17 to 1.53) Autonomic neuropathy: 39/80 (49%) vs. 52/80 (65%); RR 0.53 (95% CI 0.34 to 0.81) Peripheral neuropathy: 44/80 (55%) vs. 46/80 (58%); RR 0.97 (95% CI 0.62 to 1.51)					
UKPDS							
Holman 2008[155] UKPDS	All-cause mortality Diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction) Diabetes-related death (fatal MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia or sudden death) Fatal or nonfatal stroke Peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease) Microvascular disease (vitreous hemorrhage, retinal photocoagulation, renal failure) All-cause mortality Diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart	**A vs B** All-cause mortality: 373/758 (49%) vs 211/390 (54%); RR 0.89 (95% CI 0.75 to 1.06) Diabetes-related death: 203/758 (27%) vs 122/390 (31%); RR 0.84 (95% CI 0.67 to 1.05) Any diabetes-related endpoint: 466/758 (61%) vs 248/390 (64%); RR 0.93 (95% CI 0.80 to 1.09) MI: 205/758 (27%) vs 115/390 (29%); RR 0.90 (95% CI 0.71 to 1.13) Stroke: 90/758 (12%) vs 58/390 (15%); RR 0.77 (95% CI 0.55 to 1.07) Peripheral vascular disease: 21/758 (3%) vs 21/390 (5%); RR 0.50 (95% CI 0.28 to 0.92) Microvascular disease: 141/758 (19%) vs 82/390 (21%); RR 0.84 (95% CI 0.64 to 1.10) **A vs C** All-cause mortality: 1162/2729 (43%) vs 537/1138 (47%); Risk Ratio 0.87 (95% CI 9.79 to 0.96) Diabetes-related death: 618/2729 (23%) vs 297/1138 (26%); Risk Ratio 0.83 (95% CI 0.73 to 0.96) Any diabetes-related endpoint: 1571/2729 (58%) vs 686/1138 (60%); Risk Ratio 0.91 (95% CI 0.83 to 0.99) MI: 678/2729 (25%) vs 319/1138 (28%); Risk Ratio 0.85 (95% CI 0.74 to 0.97) Stroke: 260/2729 (10%) vs 116/1138 (10%); Risk Ratio 0.91 (95% CI 0.73	NR	NR	Good	UK Medical Research Council, UK Department of Health, Diabetes UK, British Heart Foundation, Bristol Meyers Squibb, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, Pfizer	

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
	failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction) Diabetes-related death (fatal MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia or sudden death) Fatal or nonfatal stroke Peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease) Microvascular disease (vitreous hemorrhage, retinal photocoagulation, renal failure)	to 1.13) Peripheral vascular disease: 83/2729 (3%) vs 40/1138 (4%); Risk Ratio 0.82 (95% CI 0.56 to 1.19) Microvascular disease: 429/2729 (16%) vs 222/1138 (20%); Risk Ratio 0.76 (95% CI 0.64 to 0.89) **B vs C** All-cause mortality: 152/342 (44%) vs 217/411 (53%); Risk Ratio 0.73 (95% CI 0.59 to 0.89) Diabetes-related death: 81/342 (24%) vs 120/411 (29%); Risk Ratio 0.70 (95% CI 0.52 to 0.92) Any diabetes-related endpoint: 209/342 (61%) vs 262/411 (64%); Risk Ratio 0.79 (95% CI 0.66 to 0.95) MI: 81/342 (24%) vs 126/411 (31%); Risk Ratio 0.67 (95% CI 0.51 to 0.89) Stroke: 34/342 (10%) vs 42/411 (10%); Risk Ratio 0.80 (95% CI 0.50 to 1.27) Peripheral vascular disease: 13/342 (4%) vs 21/411 (5%); Risk Ratio 0.63 (95% CI 0.32 to 1.27) Microvascular disease: 66/342 (19%) vs 78/411 (19%); Risk Ratio 0.84 (95% CI 0.60 to 1.17) **A and B vs C** All-cause mortality: 1314/3071 (43%) vs 754/1549 (49%); RR 0.88 (95% CI 0.82 to 0.94) Diabetes-related death: 699/3071 (23%) vs 417/1549 (27%); RR 0.85 (95% CI 0.76 to 0.94) Any diabetes-related endpoint: 1780/3071 (58%) vs 948/1549 (61%); RR 0.95 (95% CI 0.90 to 0.995) MI: 759/3071 (25%) vs 445/1549 (29%); RR 0.86 (95% CI 0.78 to 0.95) Stroke: 294/3071 (10%) vs 158/1549 (10%); RR 0.94 (95% CI 0.78 to 1.13) Peripheral vascular disease: 96/3071 (3%) vs 61/1549 (4%); RR 0.79 (95%					

Appendix B10. Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use in Persons With DM Not Specifically Screen-Detected

Author Year Study Name	Outcomes Assessed	Clinical Health Outcomes	Subgroups	Adverse Events	Quality Rating	Funding Source	Comments
		CI 0.58 to 1.09) Microvascular disease: 495/3071 (16%) vs 300/1549 (19%); RR 0.83 (95% CI 0.73 to 0.95)					
VADT							
Duckworth, 2009[156] VADT	Cardiovascular morbidity and mortality, retinopathy, neuropathy	**A vs B** All-cause mortality: 102/892 (11%) vs. 95/899 (11%); HR 1.07 (95% CI 0.81 to 1.42) CV mortality: 40/892 (5%) vs. 33/899 (4%); HR 1.32 (95% CI 0.81 to 2.14) Neoplastic mortality: 24/892 (3%) vs. 21/899 (2%); RR 1.15 (95% CI 0.65 to 2.05) Non-CV, non-neoplastic mortality: 38/892 (4%) vs. 41/899 (5%); RR 0.93 (95% CI 0.61 to 1.44) Sudden death: 11/892 (1%) vs. 4/899 (0.4%); RR 2.77 (95% CI 0.89 to 8.67) Incident retinopathy: 54/128 (42%) vs. 66/135 (49%); RR 0.86 (95% CI 0.66 to 1.13) Any increase in albuminuria: 63/693 (9%) vs. 97/703 (14%); RR 0.66 (95% CI 0.49 to 0.89) Any incident neuropathy: 202/464 (44%) vs. 218/498 (44%); RR 0.99 (95% CI 0.86 to 1.15)	NR	A vs. B Any serious adverse event: 24.1% (215/892) vs. 17.6% (158/899); RR 1.37, 95% CI 1.14 to 1.65 Hypoglycemia: 11.0% (98/892) vs. 7.2% (65/899); RR 1.52, 95% CI 1.13 to 2.05 Withdrawal due to adverse event: 0.8% (7/892) vs. 0.3% (3/899); RR 2.35, 95% CI 0.61 to 9.07	Good	Department of Veterans Affairs Office of Research and Development; National Institutes of Health; American Diabetes Association; Roche Pharmaceuticals; GlaxoSmithKline; sanofi-aventis; Amylin; Novo Nordisk; Roche Diagnostics; Kos Pharmaceuticals; Takeda Pharmaceuticals	

Abbreviations: ACCORD = Action to Control Cardiovascular risk in Diabetes; ADVANCE =The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AE=adverse event; AHR = aryl hydrocarbon receptor; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CDC = Centers for Disease Control and Prevention; CHD = coronary heart disease; CHF = coronary heart failure; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; DSC = diabetes self-care; DTSQ = diabetes treatment satisfaction questionnaire; GI = gastrointestinal ; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; HR = hazard ratio; HRQL = health-related quality of life; HRQOL = health-related quality of life; IFG = impaired fasting glucose; JEDIT = The Japanese elderly Diabetes Intervention Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; LDL = low density lipoprotein; LVH = left ventricular hypertrophy; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese ;MI = myocardial infraction; mm Hg = millimeters of mercury; NHLBI = National Heart, Lung and Blood Institute; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SANDS=Stop Atherosclerosis in Native Diabetics Study; SBP = systolic blood pressure; TC = total cholesterol; TIA = transient ischemic attack; UK = United Kingdom; UKPDS = United Kingdom Prospective Diabetes Study; US = United States; VADT = Veterans Affairs Diabetes Trial; WHO = World Health Organization

Appendix B11. Quality Assessment of Trials of More Versus Less Intensive Glucose, Blood Pressure, Lipid Control, or Aspirin Use

Study Name	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze People in the Groups in Which They Were Randomized?	Quality Rating
ADDITION[68]	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No/No	Yes	Fair
ACCORD 2008 (including substudies)[79,127-129,139-144,174]	Yes	Yes	Yes	Yes	Yes	Yes-lipid trial No- blood pressure trial	Yes-lipid trial No- blood pressure trial	Yes-intervention period	No/No	Yes	Good
ADVANCE 2007[80,126,130,145-147]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
JEDIT[148]	Unclear	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
JPAD[149,150]	Yes	No	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Fair
MEGA 2006[84,151]	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
SANDS 2008[152]	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Good
Steno-2 2008[153]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Good
UKPDS 1998[154,155]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Good
VADT 2009[156]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Good

Abbreviations: ADDITION = The Anglo-Danish-Dutch Study of Intensive Treatment In People With Screen-Detected Diabetes; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; JEDIT = The Japanese Elderly Diabetes Intervention Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

Appendix B12. Summary of Trials of Intensive Glucose Control Included in Systematic Reviews

	Systematic Reviews									
Trials	Coca 2012[116] (7 studies)[a]	Hemmingsen 2012[115] (20 studies)	Boussageon 2011[118] (11 studies)[a]	Castagno 2011[119] (7 studies)	Hemmingsen 2011[117] (14 studies)	Kelly 2009[121] (5 studies)[a]	Ma 2009[123] (8 studies)	Wu 2010[120] (6 studies)[a]	Ray 2009[122] (5 studies)	Mannucci 2009[124] (5 studies)
ACCORD 2008	x	x	x	x	x	x	x	x	x	x
ADVANCE 2008	x	x	x	x	x	x	x	x	x	x
Bagg 2001		x			x					
Becker 2003		x			x					
Dargie 2007			x							
DIGAMI 2 2005		x								
Guo 2008		x								
IDA 2009		x			x					
HOME 2009			x							
Jaber 1996		x			x					
Kumamoto 2000	x	x	x		x		x	x		
Lu 2010		x			x					
Melidonis 2000		x								
PROActive 2005			x	x			x		x	x
RECORD 2009				x						
REMBO 2008		x			x					
Service 1983		x			x					
Stefanidis 2003		x								
Steno-2 2008		x					x			
UGDP 1975		x	x		x					
UKPDS 1998	x	x	x	x	x	x	x	x	x	x
VA CSDM 1995	x	x	x	x	x		x	x		
VADT 2009	x	x	x	x	x	x	x	x	x	x
Yang 2007		x								

[a]Results from multiple publications analyzed separately.

Abbreviations: ACCORD = Action to Control Cardiovascular risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; DIGAMI =The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; IDA = International Diabetes Atlas; HOME = Hyperinsulinaema: the Outcome of Its Metabolic Effects; ProActive = The Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; REMBO = rational effective multicomponent therapy; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; VA CSDM = Veterans Affairs Cooperative Study in Diabetes Mellitus; VADT = Veterans Affairs Diabetes Trial.

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion and Exclusion Criteria
Armato, 2012[165]	Prospective cohort	Single center United States	A. Pioglitazone 15 mg/day and metformin 850 mg/day (n=40) B. Pioglitazone 15 mg/day, metformin 850 mg/day, and exenatide 10 mcg/twice daily (n=47) C. Lifestyle counseling, including weight loss 7% over 3 months, diet information, walking 30 minutes per day 7 days per week (n=18)	**A vs. B vs. C** Mean followup: 6.9 vs. 5.5 vs. 8.9 months	**A vs. B vs. C** Mean age: 62 vs. 56 vs. 61 years; p=0.03 Female sex: 28% vs. 43% vs. 39% Race: 82.5% white, 2.5% black, 15% other vs. 83% white, 2.1% black, 14.9% other vs. 100% white Mean BMI: 27.0 vs. 29.7 vs. 27.5 HbA1c: 5.8 vs. 5.7 vs. 5.6	Patients with IFG or IGT Exclude: Patients with normal insulin sensitivity and normal cell function (patients with normal insulin sensitivity plus moderate reduction in cell function or normal cell function plus moderate reduction in insulin sensitivity were not offered pharmacotherapy)
DeFronzo, 2011[98] ACT NOW	RCT	8 centers United States	A. Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) B. Placebo (n=299)	Median followup: 2.4 years	**A vs. B** Mean age: 53 vs. 52 years Female sex: 58% vs. 58% Race: 51% White, 26% Hispanic, 19% Black, 3% other vs. 57% White, 25% Hispanic, 15% Black, 3% other Mean BMI: 33.0 vs. 34.5 Mean HbA1c: 5.5 vs. 5.5	Patients age ≥18 years with impaired glucose tolerance (fasting plasma glucose 95 to 125 mg/dL), BMI ≥25, and ≥1 other risk factors for diabetes Exclude: Diabetes; previous treatment with thiazolidinedione (ever), metformin (within 1 year prior to randomization), or sulfonylureas, meglitinide, alpha glucosidase inhibitors, or insulin for >1 week within prior year or within 3 months prior to randomization; cardiovascular disease, hospitalization for treatment of heart disease or stroke in past 6 months; NYHA class >2; left bundle branch block or 3rd-degree AV block; aortic stenosis; SBP >180 mmHg or DBP >105 mmHg; renal disease; anemia; hepatitis; gastrointestinal disease; recent or significant abdominal surgery; pulmonary disease with dependence on oxygen or daily use of bronchodilators; chronic infection; weight loss >10% of body weight in past 6 months; current or anticipated pregnancy; major psychotic disorders;

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion and Exclusion Criteria
						excessive alcohol intake; thyroid disease; other endocrine disorders; fasting plasma triglyceride >400 mg/dL; history of bladder cancer
Katula, 2013[172]	RCT	Community setting United States	A. Intensive lifestyle intervention (n=151) B. Usual care (n=150)	Treatment duration: 24 months	**A vs. B** Mean age: 57.3 vs. 58.5 years Female sex: 58% vs. 57% Race: 73.5% White, 25.8% Black, 0.7% other vs. 74% White, 23.3% Black, 2.7% other Mean BMI: 32.8 vs. 32.6	Overweight or obese patients with impaired fasting glucose Exclude: diabetes, CVD within past 6 months, uncontrolled hypertension, pregnancy, chronic use of medication likely to affect glucose metabolism, chronic disease likely to limit life span to <2-3 years
Kawamori, 2009[101]	RCT	103 centers Japan	A. Voglibose 0.2 mg/day (n=897) B. Placebo (n=881)	Study duration: 5 years Mean followup: 3 years	**A vs. B** Mean age 55.7 vs. 55.7 years Female sex: 40% vs. 40% Race: NR	Ages 30-70, FPG <6.9 mmol/L, 2hr OGTT 7.8-11.0 mmol/L, hbA1c <6.5, and one RF from metabolic syndrome or FHx Exclude: diabetes and disease likely to impair GT
Li, 2008[102] See also: Li, 2014[110] Da Qing	RCT (cluster)	33 centers China	A. Combined lifestyle, diet, or lifestyle + diet diet interventions: increase vegetable intake and lose weight by decreasing calories from sugar and alcohol; increase leisure time and physical activity (n=438) B. Control (n=138)	20 year followup of Da Qing study Mean followup: 9.4 years intervention weekly for 1m, monthly for 3 m and every 3months after that for remainder of the study (6 years)	**A vs. B** Mean age: 45 vs. 47 years Female sex: 47% vs. 43% Race: NR Mean BMI: 25.7 vs. 26.2	Patients aged >25 years, with IGT Exclude: NR
Lindalhl, 2009[171] VIP	RCT	Single center Sweden	A. Intensive lifestyle intervention (n=83) B. Usual care (n=85)	Treatment duration: 1 year Followup: 5 years	**A vs. B** Mean age: 52 vs. 54 years Female sex: 70% vs. 61% Race: NR Mean BMI: 31.2 vs. 30.2	Patients with IGT and BMI >27
Lindblad, 2011[168]	RCT	23 centers Sweden	A. Glimepiride 1 mg/day (n=136) B. Placebo (n=138)	Mean followup: 3.7 years	**A vs. B** Mean age: 60.4 vs. 59.6 years Female sex: 35.3% vs. 45.7% Race: NR Mean BMI: 29.9 vs. 29.6 Mean HbA1c: 4.9 vs. 4.9	Patients aged 40-70 years with IFG Exclude: MI or stroke during previous 12 months, heart failure, endocrine disease or other disease that would hamper participation

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion and Exclusion Criteria
Lu, 2011[166]	RCT	4 communities China	A. IGT - acarbose 50 mg/3 times daily; IFG or IGT/IFG - metformin 250 mg/3 times daily; antihypertensive agents, antidyslipidemia agents, and aspirin (n=95) B. Control - health/diabetic education once a month (n=86)	2 years	**A vs. B** Mean age: 62 vs. 65 years Female sex: 47% vs. 48% Race: NR Mean BMI: 27.1 vs. 26.9 HbA1c: 5.9 vs. 6.0	Patients aged 40 to 80 years, BMI ≥19, with impaired glucose regulation (IFG/IGT) Exclude: Pregnant or lactating women, women of childbearing age not using contraception, previous diabetes diagnosis, major debilitating disease, any major cardiovascular event within the prior 6 months, treatment with systemic glucocorticoids in the prior 3 months, emotional disorders, or substance abuse disorder
NAVIGATOR, 2010[103]	RCT	806 centers 40 countries	A. Nateglinide 60 mg/3 times daily (n=4645) B. Placebo (n=4661) *Patients also randomized in 2x2 factorial design to receive valsartan or placebo	Median followup: 5.0 years	**A vs. B** Mean age: 64 vs. 64 years Female sex: 51% vs. 50% Race: 83% White, 2.6% Black, 6.7% Asian, 7.8% other vs. 83.2% White, 2.5% Black, 6.5% Asian, 7.8% other Mean BMI: 30.5 vs. 30.5 HbA1c: 5.8 vs. 5.8	Patients with IGT, fasting plasma glucose between 95 and 126 mg/dL, and one or more cardiovascular risk factor or known cardiovascular disease (for subjects aged ≥55 years) Exclude: Patients who had taken antidiabetic medication in the prior 5 years, had abnormal laboratory test results, or had concominant conditions that could interfere with assessment

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion and Exclusion Criteria
NAVIGATOR, 2010[104]	RCT	806 centers 40 countries	A. Valsartan 160 mg/once daily (n=4631) B. Placebo (n=4675) *Patients also randomized in 2x2 factorial design to receive nateglinide or placebo	Median followup: 5.0 years	**A vs. B** Mean age: 64 vs. 64 years Female sex: 50% vs. 51% Race: 83.1% White, 2.4% Black, 6.4% Asian, 8.0% other vs. 83.1% White, 2.6% Black, 6.7% Asian, 7.5% other Mean BMI: 30.4 vs. 30.6 HbA1c: 5.8 vs. 5.8	Patients with IGT, fasting plasma glucose between 95 and 126 mg/dL, and one or more cardiovascular risk factor or known cardiovascular disease (for subjects aged >55 years) Exclude: Patients who had taken antidiabetic medication in the prior 5 years, had abnormal laboratory test results, or had concominant conditions that could interfere with assessment
Nijpels, 2008[105] DAISI	RCT	Single center The Netherlands	A. Acarbose 50 mg/3 times daily (n=60) B. Placebo (n=58)	3 years and one month	**A vs. B** Mean age: 59 vs. 57 years Female sex: 49% vs. 50% Race: NR Mean BMI: 28.4 vs. 29.5 HbA1c: 5.9 vs. 5.6	Patients aged 45 to 70 years, with fasting plasma glucose $\geq$7.8 mmol/L, a 2-hour plasma glucose of 8.6-11.1 mmol/L, and HbA1c $\leq$7.0 Exclude: Patients who failed to complete the 6-week qualification period, in which acarbose doses were up-titrated over three weeks to 50 mg/three times daily and maintained for three weeks
Penn, 2009[169] EDIPS	RCT	Single center United Kingdom	A. Biweekly sessions for 1 month and monthly for 3 months, and every 3m for up to 5 years; Motivational interview from dietician and physiotherapist with quarterly newsletter and advice to target >50% energy from carbohydrate (n=51) B. One session of health promotion advice (n=51)	Study duration: 5 years Median followup: 3.1 yrs	**A vs. B** Mean age: 56.8 vs. 57.4 years Female sex: 59% vs. 61% Race: NR	IGT 7.8mmol/l-11.1, age >40, BMI>25 Exclude: diabetes, chronic illness, and impaired physical activity , or inability to participate in special diet for medical reasons
Ramachandran, 2009[106] IDPP-2	RCT	Community/occupational setting India	A. Pioglitazone (n=181) B. Placebo (n=186)	Mean follow up: 3 years	**A vs. B** Mean age 45.1 vs. 45.5 Female sex: 13% vs. 14% Race:NR	Ages 35-55, IGT 7.8-11.1 mmol/L Exclude: coronary artery disease, stroke history, major Q wave abnormality, liver disorders, kidney disorders

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Study Design	No. of Centers, Country	Interventions	Study Duration Mean Followup	Baseline Demographics	Inclusion and Exclusion Criteria
Rasmussen, 2008[167] ADDITION	RCT (cluster)	Multicenter (number NR) Denmark	A. Intensive management, including lifestyle advice, aspirin, drug treatment of blood glucose, blood pressure, and lipids according to strict targets (n=865) B. Standard care (n=645)	3 years	**A vs. B** IFG Mean age: 60 vs. 60 years Female sex: 43% vs. 43% Race: NR Mean BMI: 29.1 vs. 29.1 IGT Mean age: 61 vs. 61 years Female sex: 53% vs. 60% Race: NR Mean BMI: 29.5 vs. 29.8	Patients with IGT or IFG, aged 40 to 69 years who were high risk based on a self-administered questionnaire Exclude: Patients with severe concurrent illnesses, alcohol abuse, or who moved to general practices not participating in the study
Saito, 2011[107]	RCT	38 hospitals and clinic centers in Zensharen, Japan	A. Individual session and goal to decrease BW by 5% with follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months (n=330) B. One session advise to reduce BW by 5% (n=311)	Study duration: 3 years Mean followup: 2.7 years	**A vs. B** Mean age: 50 vs. 48 Female sex: 28% vs. 29% Race: NR	FPG 100-125 mg/dL, BMI >24, age 30-60 Exclude: diabetes, ischemic heart disease, stroke, chronic hepatitis, liver cirrhosis, chronic pancreatitis, chronic nephritis, pituitary disease, thyroid disease, adrenal gland disease, mental illness, gastrectomy, advanced malignant tumor
Sakane, 2011[170] JDPP	RCT	32 community health & company clinics Japan	A. Individual and group sessions: 4 group sessions lasting 2-3 hrs, biannual individual session lasting 20-40 min (n=146) B. One group session (n=150)	Study duration: 3 years (mean or median followup NR)	**A vs. B** Mean age: 51 years Female sex: 50% vs. 49% Race: NR	IGT, age 30-60 Exclude: Diabetes, gastrectomy, ischemic heart disease, definitive liver and kidney disease, autoimmune disease, heavy alcohol use, already adopting life style modification
Zinman, 2010[109] CANOE	RCT	2 centers Canada	A. Metformin 500 mg plus rosiglitazone 2 mg/twice daily as a fixed dose combination (n=103) B. Placebo (n=104)	Median followup: 3.9 years	**A vs. B** Mean age: 50 vs. 55 years Female sex: 65% vs. 68% Race: 74.8% White, 7.8% South Asian, 6.8% Latino, 10.7% other vs. 74% White, 6.8% South Asian, 6.7% Latino, 12.5% other Mean BMI: 31.3 vs. 32.0	Residents of Ontario, Canada, age 30-75 years (18-75 years for those of Canadian native ancestry), with ≥1 risk factor for diabetes, diagnosed with IGT based on fasting plasma glucose test and OGTT Exclude: Current use of metformin or rosiglitazone, previous use of an anti-diabetes medication (except to treat gestational diabetes), significant hepatic disease, or renal dysfunction

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup	Definition of Diabetes	Progression to Diabetes	Adverse Events	Quality Rating	Funding Source
Armato, 2012[165]	Screened: 630 Eligible: 181 Enrolled: 105 Analyzed: 105	OGTT, using ADA criteria	**A vs. B vs. C** Incidence: 0 vs. 0 vs. 5.6% (1/18); A vs. C, RR 0.15, 95% CI 0.01 to 3.62; B vs. C, RR 0.13, 95% CI 0.01 to 3.10	NR	Fair	Providence Little Company
DeFronzo, 2011[98] ACT NOW	Screened: 1827 Eligible: NR Enrolled: 602 Analyzed: **A vs. B** Withdrawal: 29.7% (90/303) vs. 23.7% (71/299) Loss to followup: 9.2% (28/303) vs. 7.4% (22/299)	OGTT confirmation of FPG or 2-hour plasma glucose, using WHO criteria	**A vs. B** Incidence: 5.0% (15/303) vs. 16.7% (50/299); RR 0.30, 95% CI 0.17 to 0.52 Annual average incidence: 2.1% vs. 7.6%; p<0.001 HR: 0.28 (95% CI 0.16 to 0.49) NNT for duration of trial (2.2 years): 8 NNT for one year: 18	**A vs. B** Any adverse event: 49.8% (151/303) vs. 40.5% (121/299); RR 1.23, 95% CI 1.03 to 1.47 Death: 1.0% (3/303) vs. 0.3% (1/299); RR 2.96, 95% CI 0.31 to 28.30	Fair	Takeda Pharmaceuticals
Katula, 2013[172]	Screened: 743 Eligible: 326 Enrolled: 301 Analyzed: 301 **A vs. B** Withdrawal: 1% (2/151) vs. 3% (5/150)	HOMA IR (fasting insulin x fasting glucose/22.5)	**A vs. B** Incidence at 12 months: 1.3% (2/151) vs. 4% (6/150); RR 0.33, 95% CI 0.07 to 1.61 Incidence at 24 months: 2.6% (4/151) vs. 7.3% (11/150); RR 0.36, 95% CI 0.12 to 1.11	NR	Fair	National Institute of Diabetes and Digestive and Kidney Diseases
Kawamori, 2009[101]	Screened: 4582 Eligible: NR Enrolled: 1780 Analyzed: 1778 **A vs. B** Withdrawal: 14.4% (129/897) vs. 16.5% (146/883)	HbA1c >6.5% and two occasions of one of the following: 2-hour glucose >11 mmol/L, FPG >7.0 mmol/L, or random glucose >11 mmol/L (same as WHO criteria + HbA1c)	**A vs. B** 5.5% (50/897) vs. 12% (106/881); RR 0.46, 95% CI 0.34 to 0.64 HR: 0.595 (voglibose group had 40% lower chance of developing diabetes compared to placebo) Progression rate for TG: 30.2% and 36.2% for controls after 144 weeks	**A vs. B** Withdrawal due to adverse events: 7.4% (66/897) vs. 6.2% (55/883) Any adverse event: 90% (810/897) vs. 85% (750/881) Serious adverse event: 0.6% (5/897) vs. 0.2% (2/881) Death 0.7% (6/897) including 1 MI vs 0% (0/881)	Good	Takeda Pharmaceuticals

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup	Definition of Diabetes	Progression to Diabetes	Adverse Events	Quality Rating	Funding Source
Li, 2008[102] See also: Li, 2014[110] Da Qing	Screened: 110,660 Eligible: NR Enrolled: 577 Analyzed: 530 Withdrawal: 7 Loss to followup: 40	Self-reported diagnosis, medical records, or FPG or OGTT testing, using WHO criteria (1985 version)	**A vs. B** End of treatment Incidence: 7.9 vs. 14.1 cases/100 person-years per year Cumulative incidence: 42.8% (187/438) vs. 65.8% (90/138) Adjusted HR: 0.49 (95% CI 0.33 to 0.73) 20-year followup Incidence: 6.9 vs. 11.3 cases/100 person-years per year Cumulative incidence: 79.7% (349/438) vs. 92.8% (128/138); RR 0.86, 95% CI 0.80 to 0.92 Adjusted hazard rate ratio: 0.57, 95% CI 0.41 to 0.81 NNT: 6 23-year followup Incidence: 73% (312/430) vs. 90% (124/138); 7.3 vs. 12.3 cases/100 person-years per year; HR 0.55 (95% CI 0.40 to 0.76)	Active intervention period: CVD and mortality outcomes - see KQ3	Fair	World Health Organization, Centers for Disease Control and Prevention, China-Japan Friendship Hospital, and Da Qing First Hospital
Lindalhl, 2009[171] VIP	Screened: 28,000 Eligible: 650 Invited: 650 Enrolled: 301 (101 enrolled as "substitutes") Analyzed: 168 **A vs. B** Withdrawal: 13.2% (20/151) vs. 9.3% (14/150) Loss to followup: 17% (17/100) vs. 9.6% (9/94)	OGTT using WHO criteria	**A vs. B** Incidence at one year (end of intervention): 6% (5/83) vs. 23.5% (20/85); RR 0.26, 95% CI 0.10 to 0.65 Incidence at three years: 14.5% (12/83) vs. 23.5% (20/85); RR 0.61, 95% CI 0.32 to 1.18 Incidence at five years: 20% (17/83) vs. 27% (23/85); RR 0.75, 95% CI 0.44 to 1.31	NR	Fair	Joint Committee of the Northern Sweden health Care Region, the Swedish Public Health Institute, and Vasterbotten County Council
Lindblad, 2011[168]	Screened: NR Eligible: NR Enrolled: 288 Analyzed: 274 Withdrawal: 4.9% (14/288)	Two consecutive FPG >6.1 mmol/L	**A vs. B** Incidence: 30.1% (41/136) vs. 39.9% (55/138); RR 0.76, 95% CI 0.55 to 1.05 Incidence, adjusted for baseline HbA1c, proinsulin, and CRP: OR 0.62 (p=0.028)	NR	Fair	Nepi Foundation, Skaraborg Institute, FORSS Foundation

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup	Definition of Diabetes	Progression to Diabetes	Adverse Events	Quality Rating	Funding Source
Lu, 2011[166]	Screened: 2344 Eligible: 210 Enrolled: 210 Analyzed: 184 **A vs. B** Loss to followup: 9.4% (10/106) vs. 17.3% (18/104) Withdrawal due to adverse event: 1 vs. 0	OGTT using ADA criteria	**A vs. B** Incidence: 0% vs. 5.8% (5/86); RR 0.08, 95% CI 0.00 to 1.42 Incidence, metformin group: 0% vs. 12.2% (5/41); RR 0.08, 95% CI 0.00 to 1.42 Incidence, acarbose group: 0% vs. 6.7% (3/45); RR 0.13, 95% CI 0.01 to 2.48	1 participant discontinued due to a gastrointestinal reaction after taking metformin	Fair	NR
NAVIGATOR, 2010[103]	Screened: 43502 Eligible: 9518 Enrolled: 9518 Analyzed: 9306 **A vs. B** Withdrawal: 3.5% (163/4645) vs. 3.1% (143/4661) Loss to followup: 9.6% (446/4645) vs. 9.8% (459/4661)	OGTT confirmation of FPG or 2-hour glucose levels, using WHO criteria	**A vs. B** Incidence: 36.0% (1647/4645) vs. 33.9% (1580/4661); RR 1.05, 95% CI 0.99 to 1.11 Absolute hazard difference: 6.18 (95% CI 0.47 to 11.90) Hazard Ratio: 1.07 (95% CI 1.00 to 1.15)	**A vs. B** Discontinued due to adverse event: 11.2% (520/4645) vs. 10.4% (485/4661) Hypoglycemia: 19.6% (911/4645) vs. 11.3% (527/4661) CVD and mortality outcomes - see KQ3	Good	Novartis Pharma
NAVIGATOR, 2010[104]	Screened: 43502 Eligible: 9518 Enrolled: 9518 Analyzed: 9306 **A vs. B** Withdrawal: 3.3% (151/4631) vs. 3.3% (155/4675) Loss to followup: 9.4% (437/4631) vs. 10.0% (468/4675)	OGTT confirmation of FPG or 2-hour glucose levels, using WHO criteria	**A vs. B** Incidence: 33.1% (1532/4631) vs. 36.8% (1722/4675); RR 0.90, 95% CI 0.85 to 0.95 Absolute hazard difference: -12.6 (95% CI -18.4 to -6.9) Hazard Ratio: 0.86 (95% CI 0.80 to 0.92)	**A vs. B** Discontinued due to adverse event: 12.0% (556/4631) vs. 11.4% (531/4675) Hypoglycemia: 42.4% (1936/4631) vs. 35.9% (1678/4675) CVD and mortality outcomes - see KQ3	Good	Novartis Pharma

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup	Definition of Diabetes	Progression to Diabetes	Adverse Events	Quality Rating	Funding Source
Nijpels, 2008[105] DAISI	Screened: 6651 Eligible: 171 Enrolled: 118 (53 failed qualification period) Analyzed: 118 **A vs. B** Loss to followup: 0% vs. 1.7% (1/58)	FPG and 2-hour glucose using WHO criteria	**A vs. B** Incidence: 18.3% (11/60) vs. 24.1% (14/58); RR 0.76, 95% CI 0.38 to 1.53 Attributable risk: -0.14 (95% CI -0.46 to 0.21) Absolute risk reduction: 6% (95% CI -9% to 21%)	**A vs. B** Withdrawal due to adverse events: 36.7% (22/60) vs. 13.8% (8/58); RR 2.66, 95% CI 1.29 to 5.48 Death: 1.7% (1/60) vs 5.2% (3/58)	Fair	Bayer Healthcare AG
Penn, 2009[169] EDIPS	Screened: 1567 Eligible: NR Enrolled: 102 Analyzed: 42 **A vs. B** Loss to followup: 35% (18/51) vs. 29% (15/51)	Two OGTTs, using WHO criteria	**A vs. B** Incidence: 9.8% (5/51) vs. 21.6% (11/51); RR 0.45, 95% CI 0.17 to 1.21 Incidence rate per 1,000 persons: 32.7 vs. 67.1	NR* *1 death in foot note in one table not explained in the study	Fair	Wellcome Trust
Ramachandran, 2009[106] IDPP-2	Screened: 6589 Enrolled: 407 Analyzed: 367 **A vs. B** Loss to followup: 11.3% (21/181) vs. 8.4% (16/186)	OGTT using WHO criteria	**A vs. B** **C**umulative incidence: 29.8% (54/181) vs. 31.6% (59/186); RR 0.94, 95% CI 0.69 to 1.28	A: 2 deaths due to cardiac arrest B: 1 death due to road accident A: 2 occurrence of heart disease requiring admission B: 1 occurrence of heart disease requiring admission A: 4 major other adverse events B: 10 other major adverse events	Fair	India's Diabetes Research Foundation
Rasmussen, 2008[167] ADDITION	Screened: NR Eligible: 1821 Enrolled: 1821 Analyzed: 1821 Withdrawal: 4.5% (77/1722) Loss to followup: 12.3% (212/1722)	OGTT using WHO criteria	**A vs. B** Incidence: 14.1 vs. 15.8 cases/100 person-years; RR 0.89, 95% CI 0.78 to 1.02 **Subanalyses** Motivational interviewing + intensive intervention: RR 0.83, 95% CI 0.68-1.00 Intensive treatment alone: RR 0.95, 95% CI 0.80 to 1.14 IFG: RR 0.90, 95% CI 0.73 to 1.12 IGT: RR 0.90, 95% CI 0.77 to 1.07	During screening portion of trial, 1.2% (22/1821) died	Fair	Danish Centre for Evaluation and Health Technology Assessment; Danish Research Foundation for General Practice; Danish National Board of Health; Danish Medical Research Council; Danish Diabetes Association

Appendix B13. Studies of Interventions to Prevent or Delay Progression to DM

Author, Year Study Name	Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup	Definition of Diabetes	Progression to Diabetes	Adverse Events	Quality Rating	Funding Source
Saito, 2011[107]	Enrolled: 641 Analyzed: 562 **A vs. B** Post-randomization Loss to followup: 14.1% (44/311) vs. 10.6% (35/330)	OGTT using WHO criteria	**A vs. B** Cumulative incidence: 10.6% (35/330) vs. 16.4% (51/311); RR 0.65, 95% CI 0.43 to 0.97	No adverse events *1 death in LTF in intervention group not explained	Fair	All Japan Federation of Social Insurance Associations
Sakane, 2011[170] JDPP	Screened: 1279 Eligible: 304 Enrolled: 296 Analyzed: 213 **A vs. B** Post-randomization exclusions: 3.9% (6/152) vs. 1.3% (2/152) Withdrawal: 29% (43/146) vs. 27% (40/150)	OGTT using WHO criteria	**A vs. B** Incidence: 6.1% (9/146) vs. 12% (18/150); RR 0.51, 95% CI 0.24 to 1.11	NR	Fair	The Ministry of Health, Welfare, and Labour of Japan
Zinman, 2010[109] CANOE	Screened: 992 Eligible: 247 Enrolled: 207 Analyzed: 207 **A vs. B** Withdrawal: 12.6% (13/103) vs. 9.6% (10/104) Loss to followup: 1.9% (2/103) vs. 1.9% (2/104)	Two FPG values of >7.0 mmol/L or one 2-hour glucose or OGTT value >11.0 mmol/L (same as WHO criteria)	**A vs. B** Incidence: 13.6% (14/103) vs. 39.4% (41/104); RR 0.34, 95% CI 0.20 to 0.59 Relative risk reduction: 66% (95% CI 41-80%) Absolute risk reduction: 26% (95% CI 14-37%) NNT over 3.9 years: 4 (95% CI 2.7-7.1) Hazard ratio: 0.31 (95% CI 0.17 to 0.58)	**A vs. B** Hypoglycemia: 2% (2/103) vs. 1% (1/104); p=0.62 MI 0% (0/103) vs 1% (1/104), p=1.00 CHF 0% (0/103) vs 1% (1/104), p=1.00	Good	GlaxoSmithKline

Abbreviations: ADDITION = The Anglo-Danish-Dutch Study Of Intensive Treatment In People With Screen-Detected Diabetes; BMI = body mass index; BW = body weight; CANOE = Canadian Normoglycemia Outcomes Evaluation; CHF = coronary heart failure; CI = confidence interval; CVD = cardiovascular disease; DAISI = Dutch acarbose intervention study; DBP = diastolic blood pressure; EDIPS = European Diabetes Prevention Study; FHx = family history; GT = glucose tolerance; HbA1c = glycated hemoglobin; HR = hazard ratio; IDPP = Indian Diabetes Prevention Program; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; JDPP = Japanese diabetes prevention programme; MI = myocardial infraction; NNT = number needed to treat; NYHA = New York Heart Association; NAVIGATOR = Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; OGTT = oral glucose tolerance test; RCT = randomized controlled trial; RR = relative risk; SBP = systolic blood pressure.

Appendix B14. Quality Assessment of Trials of Interventions to Prevent or Delay Progression to DM

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup: Differential/ High?	Analyze People in the Groups in Which They Were Randomized?	Quality Rating
DeFronzo, 2011[98] ACT NOW	Unclear; likely yes (block randomization based on a 'randomization code')	Unclear	Yes	Yes	Unclear	Unclear; likely yes	Unclear; likely yes	Yes	No/No	Yes	Fair
Katula, 2013[172]	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Fair
Kawamori, 2009[101]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Li, 2014[110] Da Qing	Unclear; cluster randomization	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
Lindahl, 2009[171] VIP	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/No	No	Fair
Lindblad, 2011[168] NANSY	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
Lu, 2011[166]	Unclear	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
NAVIGATOR, 2010[104, 104]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Good
Nijpels, 2008[105] DAISI	Yes	Yes	No; not HbA1c	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
Penn, 2009[169] EDIPS	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Fair
Ramachandran, 2009[106] IDPP-2	Yes	No-sequential	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	No; ~11% randomized but not analyzed	Fair
Rasmussen, 2008[167] ADDITION	Unclear; Yes for Cambridge	Unclear; Yes for Cambridge	Yes	Yes	Yes	No	No	Yes	No/No	Yes	Fair
Saito, 2011[107]	Yes	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	Fair
Sakane, 2011[170] JDPP	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No/No	No; ~30% not analyzed	Fair
Zinman, 2010[109] CANOE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good

Appendix B15. Quality Assessment of Cohort Studies of Interventions to Prevent or Delay Progression to DM

Author, Year	Did the Study Attempt to Enroll All (or a Random Sample of) Patients Meeting Inclusion Criteria, or a Random Sample (Inception Cohort)?	Were the Groups Comparable at Baseline on Key Prognostic Factors (e.g., by restriction or matching)?	Did the Study Use Accurate Methods for Ascertaining Exposures and Potential Confounders?	Were Outcome Assessors and/or Data Analysts Blinded to the Exposure Being Studied?	Did the Article Maintain Comparable Groups?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Is There Important Differential Loss to Followup or Overall High Loss to Followup?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Armato, 2012[165]	Yes	No; not age	Yes	Unclear	Yes	Unclear	No	Yes	Fair