KAISER PERMANENTE®
NATIONAL CLINICAL PRACTICE GUIDELINES

Adult Diabetes
Clinical Practice Guidelines

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Approved by the
National Guideline Directors
January 2012

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Introduction

Kaiser Permanente's National Guideline Program

The National Guideline Program (NGP) supports the development of a core set of explicit, scientifically based clinical practice guidelines, practice resources, and evidence synopses to assist Kaiser Permanente (KP) physicians, administrators, and other health care professionals in determining the most effective medical practices.

This core set of evidence-based resources will:
- Create Programwide economies of scale,
- Support ongoing performance improvement activities,
- Consistently provide high quality resources for use in care delivery tools and systems, and
- Increase KP regions' abilities to leverage clinical guidelines to improve clinical outcomes.

Clinical practice guidance, based on scientific evidence, is essential for providing high quality care and continuously improving on it. Such guidance needs to be integrated into the electronic medical record and other decision support tools to be accessible to clinicians at the point of care. In addition, engaging our members in collaborative, shared decision-making conversations regarding their personal preferences is an essential component of patient-centered quality care. Furthermore, cost-effectiveness of various evidence-based interventions and resource limitations are important considerations. This involves addressing health problems in ways that maximize the health of the population given the available resources.

Who are the National Guideline Directors'?

The National Guideline Directors (NGD) are a group of experts and advocates of evidence-based medicine who provide direction and oversight to the National Guideline Program (NGP). In this role, the NGD selects and approves topics for evidence-based knowledge products, owns Kaiser Permanente's Common Methodology, and is responsible for quality assurance review. This group is composed of representatives from the Care Management Institute (CMI) and all eight regions.

What Is the Guideline Quality Committee?

The Guideline Quality (GQ) Committee is a subcommittee of the NGD consisting of a group of evidence experts from various KP regions and CMI who review and approve all the National Guidelines. This review ensures that the processes used to develop guideline content have adhered to KP evidence-based methods and that the labels applied to clinical recommendations therein are accurate (e.g., "evidence-based" or "consensus-based").

How Are Guidelines Developed?

Guidelines are developed with the use of an "evidence-based methodology" and involve a systematic literature search, critical appraisal of the research design and statistical results of relevant studies, and grading of the sufficiency (quantity, quality, consistency, and relevancy) of the evidence for drawing conclusions. An evidence search includes literature published in peer-reviewed scientific journals, existing evidence-based guidelines, consensus-based statements from external professional societies and government health organizations, and clinical expert opinion of KP regional specialty groups. For additional information on evidence grading, see Table 1 in Appendix A.

To develop or revise a guideline, CMI consultants work with a multidisciplinary Guideline Development Team (GDT). Each GDT consists of a core group of physicians, representing primary care and the specialties most affected by the guideline topic, and, as appropriate, other content experts from disciplines such as pharmacy, nursing, and health education. The members of a GDT are nominated by the respective National Guideline Directors to represent their regions. The GDT reviews the appraisal of the evidence and develops or revises clinical recommendations based on the current evidence. Each regional representative then presents the draft guideline recommendations to key experts and champions in their regions for critical review and support to improve the likelihood of implementation once the guideline is published.

How Often Are Guidelines Reviewed and Revised?

To keep current with changing medical practices, all guidelines are reviewed, and, if appropriate, revised at least every two years. This evidence-based guideline is based on the 2010 National Diabetes Guideline. A 2012 review of these recommendations found them to be current.

What Does It Mean for a Guideline to Be Evidence-Based?

Each clinical recommendation within a guideline is labeled as "evidence-based" or "consensus-based." A recommendation is considered "evidence-based" if there has been a systematic review of the evidence, the evidence is sufficient, and the recommendation is consistent with the evidence. A recommendation can also be considered "evidence-based" if there is insufficient evidence but either no particular intervention is recommended or options are recommended without favoring one of the options over others. A recommendation is considered "consensus-based" if there has been a systematic review of the evidence, the evidence is insufficient to support an evidence-based recommendation, and the GDT decides to make a consensus recommendation.

What Does It Mean for a Guideline to Be Approved and National?

A recommendation that is consistent with the above policies is labeled as "National Guideline Directors Approved." A recommendation that fails to satisfy those criteria is not approved and will be noted as such. A National Guideline Directors Approved guideline for which at least 90% of the recommendations are approved by at least six of the eight KP regions is a "National Guideline." On the topics for which they exist, National Guidelines are the preferred evidence source for KP HealthConnect content.

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Acknowledgments

The Kaiser Permanente (KP) National Adult Diabetes Clinical Practice Guideline is the result of the extensive clinical expertise, collaborative efforts, and outstanding personal contributions of the following participants:

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Guidelines Summary

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Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Prevention of Diabetes

1. Intervention to Delay the Onset of Type 2 Diabetes

1A For patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG),* the GDT strongly recommends that first-line therapy include methods to promote healthy eating and to increase physical activity, which are targeted to achieve a sustained weight loss (5 to 7%), and delay the onset of diabetes.

1B Lifestyle interventions alone or in combination with metformin are effective in delaying the onset of type 2 diabetes in people with pre-diabetes.

Evidence-based: A - (Intervention to Delay Onset of Type 2 Diabetes)
Evidence-based: A - (Definition of Impaired Glucose Tolerance)
Consensus-based - (Definition of Impaired Fasting Glucose)

2. Postpartum Screening for Diabetes in Women with a History of Gestational Diabetes Mellitus (GDM)

2 Screening for diabetes six weeks after delivery is recommended for women with gestational diabetes. *Consensus-based*

3. Postpartum Follow-Up of GDM

3A Information/education about the increased risk of developing type 2 diabetes following gestational diabetes is recommended for women with gestational diabetes. *Consensus-based*

3B For women with recent gestational diabetes, long-term postpartum follow-up, including advice on diet, exercise and behavior modification, is recommended to prevent future progression to type 2 diabetes. *Consensus-based*

* Included studies defined impaired glucose tolerance as a glucose level of 140 to 199 post 75 g glucose load. The ADA defines impaired fasting glucose as FPG levels ≥ 100 mg/dl (5.6 mmol/L) but < 126 mg/dl (7.0 mmol/L).(1)

Screening

4. Screening for Type 2 Diabetes

4A Screening is recommended for asymptomatic adults with sustained blood pressure > 135/80 mmHg (either treated or untreated) to establish an appropriate blood glucose target. *Evidence-based:B*

4B Screening is an option for all other adults with risk factors for diabetes.

- Age 45 years or older
- Under age 45 and overweight (BMI ≥ 25kg/m^2, may be lower in some ethnic groups) with additional risk factors:
  - physical inactivity,
  - first-degree relative with diabetes,
  - members of a high-risk ethnic population (e.g., Black/African American, Latino, Native American, Asian American, Pacific Islander),
  - women who delivered a baby weighing > 9 lb or were diagnosed with GDM,
  - hypertension (≥ 140/90 mmHg or on therapy for hypertension),
  - HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l),
  - women with polycystic ovarian syndrome (PCOS),
  - A1C ≥ 5.7%, IGT or IFG on previous testing,
  - other clinical conditions associated with insulin resistance (e.g., severe obesity [defined as BMI ≥ 40], acanthosis nigricans), and/or
  - history of cardiovascular disease

Consensus-based

4C In the absence of sufficient evidence to recommend an optimal screening frequency, regions are encouraged to set appropriate screening intervals. *Consensus-based*

5. Test to Screen for Diabetes and Pre-Diabetes

5A If a test for diabetes and pre-diabetes is desired, a Fasting Plasma Glucose (FPG) test is currently recommended. A HbA1c is also an acceptable option. *Consensus-based*

5B HbA1c is now accepted as a standard routine screening test. *Consensus-based*

Pharmacological Management of Diabetes

6. Blood Pressure Threshold to Initiate Drug Therapy in Patients with Diabetes and Hypertension

6A The GDT recommends initiating antihypertensive drug therapy in patients with diabetes with a systolic blood pressure of ≥ 140 mmHg and/or diastolic ≥ 85 to 90 mmHg. *Consensus-based*

6B After three months of lifestyle therapy, if systolic BP is 130 to 139 or diastolic BP is 80 to 89, initiate drug therapy. *Consensus-based*

7. Blood Pressure Threshold to Initiate Combination Drug Therapy in Patients with Diabetes and Hypertension

7 When BP is ≥ 150 to 160/90 mmHg, the GDT recommends initiating therapy with two drugs, either as a separate prescription or in fixed dose combinations. *Consensus-based*

Note: For patients with diabetes and hypertension, the target blood pressure is < 130/80 mmHg.

8. Initial Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease or Microalbuminuria

8A The GDT strongly recommends a thiazide-type diuretic for the treatment of diabetes and hypertension (HTN) in the absence of heart failure, known coronary heart disease, or microalbuminuria. *Evidence-based: A*

8B The GDT has determined that because most individuals with HTN and diabetes will need more than one drug to control their HTN effectively, combination therapy with HCTZ/ACE inhibitors as first-line therapy is an option. *Consensus-based*

9. Step Therapy in the Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease

9 The GDT recommends:

For two drugs: When two drugs are required for hypertension control, they should be an ACE inhibitor plus a diuretic.

For three drugs: If blood pressure is not controlled on a thiazide-type diuretic in addition to an ACE inhibitor, then treatment with a thiazide-type diuretic, an ACE inhibitor, and a beta-blocker are recommended.
Consensus-based

10. Drug Therapy for Patients with Diabetes, Hypertension, and Microalbuminuria or Diabetic Nephropathy

10 The GDT recommends that if a person with diabetes, hypertension, and microalbuminuria (or albuminuria) is intolerant to an ACE inhibitor, then, in the absence of contraindications, an ARB be substituted to prevent progression of renal disease.
Consensus-based

11. Target Blood Pressure for People with Diabetes and Hypertension

11 The GDT recommends that the target blood pressure be < 130/80 mmHg for patients with diabetes and hypertension.
Evidence-based: A – (Diastolic Blood Pressure)
Consensus-based – (Systolic Blood Pressure)

12. Drug Therapy for Microalbuminuria in Normotensive Patients

12A In normotensive adults under age 55 who have diabetes and microalbuminuria, an ACE inhibitor is recommended to prevent progression to end-stage renal disease.
Consensus-based

12B In normotensive adults with diabetes, microalbuminuria (or albuminuria) and ACE inhibitor allergy or intolerance, there is insufficient evidence to recommend for or against the use of angiotensin receptor blockers to prevent progression to end-stage renal disease.
Evidence-based: I

13. Lipid Management

13A Statin Therapy: DM and CAD

Statin therapy is recommended for all patients with diabetes and CAD.

13B Statin Therapy: Initial Dose

Initiate statin therapy with at least simvastatin 40 mg daily.*

13C Statin Therapy: Age 40 or Older

Statin therapy is recommended, regardless of baseline LDL-C. NNT = 23†

13D Statin Therapy: Age 39 or Under

For people with diabetes under age 39 or younger WITH > 1 risk factor:‡

- Statin therapy is RECOMMENDED when LDL-C > 100 mg/dL.
- Statin therapy is OPTIONAL when LDL-C < 100 mg/dL.

For people with diabetes under age 39 or younger WITHOUT risk factors:‡

- Statin therapy is RECOMMENDED when LDL-C > 130 mg/dL.
- Statin therapy is OPTIONAL when LDL-C < 130 mg/dL.

14. Lipid Management: LDL Goals

14 An LDL-C goal of < 100 mg/dL, with an optional goal of < 70 mg/dL for people with diabetes and coronary artery disease, but not for people with diabetes without coronary artery disease.

Note: In some people, a target LDL < 70 to 100 mg/dl may be difficult to achieve. In these cases, use clinical judgment to weigh the benefits and risks of intensifying drug therapy.

* Lower doses recommended for patients at high risk for rhabdomyolysis.

† For every 23 diabetics or people with coronary disease, aged 40 to 80 years, who are treated with 40 mg of simvastatin daily, for five years, one mortality or fatal or non-fatal vascular event will be prevented.

‡ Risk factors include: duration of diabetes > 10 years, HDL-C < 40 mg/dL, current smoker or family history of premature CAD [Clinical CAD or sudden death in a first-degree relative aged < 55 (men) and < 65 (women)].

Drug Therapy for Primary and Secondary Prevention of Cardiovascular Events in the General Diabetes Population

15. ACE Inhibitor Therapy for Primary and Secondary Prevention of Cardiovascular Disease (CVD) in Diabetes

15 The GDT recommends ACE inhibitors therapy for patients with diabetes aged ≥ 55 years with one or more cardiovascular risk factors (total cholesterol > 200 mg/l, HDL cholesterol ≤ 35 mg/l, hypertension, microalbuminuria, or current smoking); or a history of CVD (CAD, stroke, or peripheral vascular disease). *Evidence-based: B*

16. Aspirin Therapy in Diabetes for Prevention of CVD

16A The GDT recommends that patients with diabetes ≥ 40 years old be treated with at least 81 mg/day aspirin unless contraindicated. *Consensus-based*

16B The GDT recommends that people with aspirin allergy, bleeding tendency, age > 85, or clinically active hepatic disease are not candidates for aspirin therapy. *Consensus-based*

17. Beta-Blocker Therapy for Secondary Prevention of Cardiovascular Disease in Diabetes

17 For CAD patients, non-intrinsic sympathomimetic activity (non-ISA) beta-blocker therapy is recommended, unless contraindicated. *Consensus-based*

*Note: Drugs **without** ISA are atenolol, betaxolol, bisoprolol, carvedilol, labetolol, nadolol, metoprolol, propranolol, and timolol. Drugs **with** ISA are acebutolol, and pindolol.*

18. Multifactorial Interventions for Preventing CVD

18 The GDT recommends concurrent treatment of cardiovascular (CV) risk factors for the prevention of CV events in patients with type 2 diabetes. *Consensus-based*

19. Glucose Control

19 The GDT strongly recommends intensive glucose control in patients with diabetes age < 65 and without serious comorbidities such as CAD, CF, ESRD, blindness, amputation, stroke, and dementia. *Evidence-based: A*

20. Initial Drug Therapy for Glucose Lowering in Type 2 Diabetes

20A The GDT recommends metformin as the first-line glucose lowering drug in patients with type 2 diabetes with BMI > 27. *Evidence-based: B*

20B The GDT recommends metformin as the first-line glucose lowering drug in patients with type 2 diabetes with BMI ≤ 27. *Consensus-based*

21. Step Therapy for Glucose Control

21A Following failure to achieve goals on monotherapy, the GDT recommends more than one medication. *Consensus-based*

21B The GDT has determined that there is insufficient evidence to recommend an optimal medication combination for type 2 diabetes not controlled with a single agent. *Consensus-based*

22. Glycemic Control Target

22A An overall treatment goal of HbA1c < 7% is recommended for adults with known diabetes.[*] *Consensus-based*

22B An individualized HbA1c goal using shared decision-making is recommended.

- A less stringent treatment goal[†] is recommended for patients >65 years of age, or with significant comorbidities.[*]
- Conversely, more stringent goals are an option in individual patients.

23. Microalbumin Assessments for Patients with Diabetes and Documented Microalbuminuria on ACE Inhibitors or ARBs

23 The GDT recommends that continued monitoring of microalbumin is optional in people with diabetes and established microalbuminuria, who are on an ACE inhibitor or ARB. *Consensus-based*

24. Retinal Screening

24 The GDT recommends that diabetes patients with background retinopathy, or more severe disease, should be monitored at least annually; and those without retinopathy should be screened every one to two years. *Consensus-based*

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[*] HEDIS 2009 lists the following exclusions (comorbidities) for the HbA1c indicator < 7% goal: ≥ 65 years of age; and/or, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the current and/or prior measurement year, regardless of setting; ischemic vascular disease (IVD) in the current and/or prior measurement year, regardless of setting; and at least one encounter in the measurement year, regardless of setting, of the following — chronic heart failure (CHF); prior myocardial infarction (MI); chronic renal failure (CRF)/end-stage renal disease (ESRD); dementia; blindness; and/or, amputation.

† HEDIS 2009 offers HbA1c < 8% as a treatment goal for those not eligible for the treatment goal of < 7%. Eligibility is based on laboratory data to identify the most recent HbA1c test during the measurement year.

25. Foot Screening

25A The GDT recommends that all patients with diabetes should have a foot screening that includes a monofilament test. *Evidence-based: B*

25B Patients with an abnormal monofilament test are at a high risk for lower limb complications and are candidates for entry into a podiatry population-based foot care program, or equivalent. *Evidence-based: B*

26. Frequency of Foot Screening

26 The GDT recommends annual foot screenings for patients with diabetes. *Consensus-based*

Self-Management

27. Self-Management Education

27 The GDT recommends patient training in self-care behaviors as a component of any diabetes management program.
Evidence-based: A – (Effect on Glucose Control)
Consensus-based – (Effect on Other Outcomes)

28. Self-Monitoring of Blood Glucose in Type 1 Diabetes

28A The GDT strongly recommends that patients with type 1 diabetes monitor their blood glucose. *Evidence-based: A*

28B The GDT strongly recommends that when self-monitoring of blood glucose (SMBG) is used, results be accompanied by an appropriate adjustment in therapy.
Evidence-based: A

29. Self-Monitoring of Blood Glucose in Type 2 Diabetes

29A The GDT recommends self-monitoring of blood glucose (SMBG) for patients with type 2 diabetes. *Consensus-based*

29B When SMBG is used, the GDT recommends that results be accompanied by an appropriate adjustment in therapy. *Consensus-based*

30. Self-Titration of Insulin

30 The GDT recommends self-titration of bedtime insulin dosage for patients with type 2 diabetes to enhance glucose control. *Evidence-based: B*

Rationale Statements

Prevention of Diabetes

1. Intervention to Delay the Onset of Type 2 Diabetes

1A For patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG),* the GDT strongly recommends that first-line therapy include methods to promote healthy eating and to increase physical activity, which are targeted to achieve a sustained weight loss (5 to 7%), and delay the onset of diabetes.

1B Lifestyle interventions alone or in combination with metformin are effective in delaying the onset of type 2 diabetes in people with pre-diabetes.

Evidence-based: A - (Intervention to Delay Onset of Type 2 Diabetes)
Evidence-based: A - (Definition of Impaired Glucose Tolerance)
Consensus-based - (Definition of Impaired Fasting Glucose)

Rationale:

Evidence for Recommendation 1A: Good
Evidence for Recommendation 1B: Good

Supporting Evidence

2007 Update:

New evidence was found that did not change the existing recommendation.

- One meta-analysis (Yamaoka, Tango, 2005[3]) identified nine studies of dietary interventions alone or combined with exercise. Their report indicates that these interventions reduced 2-h plasma glucose levels and decreased the 1-year incidence of type 2 diabetes mellitus.

2005 Update:

- One cost-effectiveness analysis[4] was found of the lifestyle modification program used in the Diabetes Prevention Program.[5] The Archimedes model found that the expected 30-year cost/quality adjusted life year (QALY) of the DPP lifestyle intervention compared with doing nothing would be $143,000. Using metformin to prevent diabetes would be more cost-effective, costing about $35,400 per QALY gained. However, metformin would deliver about one-third the long-term health benefits achieved by immediate lifestyle modification. This suggests that while lifestyle modification should be recommended for high-risk people, the specific lifestyle modification program used in the DPP study may not be cost effective for a national program to implement.
- Six RCTs were found that randomized patients with impaired glucose control to various treatments including lifestyle, drug therapy, or a combination of drug therapy plus lifestyle.
- The patient populations of the included RCTs were selected based on fasting blood glucose, oral glucose tolerance test, or both. The following table illustrates the range of the inclusion criteria for impaired glucose control in the included studies:

* Included studies defined impaired glucose tolerance as a glucose level of 140 to 199 post 75 g glucose load. The ADA defines impaired fasting glucose as FPG levels ≥ 100 mg/dl (5.6 mmol/L) but < 126 mg/dl (7.0 mmol/L).[1]

Study	Inclusion Criteria for Impaired Glucose Control (IGC)
Knowler, et al.	95 to 125 mg/dL (5.3 to 6.9 mmol/L) fasting and 140 to 199 mg/dL (7.8 to 11.0 mmol) post 75 g oral glucose load
Tuomilehto, et al.	140 to 200 mg/dL (7.8 to 11.0 mmol/L) post 75 g oral glucose load
Pan, et al.	140 to 199 mg/dL (7.8 to 11.0 mmol) post 75 g oral glucose load
Li Pan, et al.	140 to 199 mg/dL (7.8 to 11.0 mmol) post 75 g oral glucose load
Chiasson, et al.	140 to 199 mg/dL (7.8 to 11.0 mmol) post 75 g oral glucose load
Heymsfield, et al.	140 to 199 mg/dL (7.8 to 11.0 mmol) post 75 g oral glucose load

- Lifestyle interventions were found to delay the onset of type 2 diabetes when compared with placebo. Metformin delays the onset of type 2 diabetes when compared with placebo but is less effective than lifestyle interventions alone. Acarbose was also found to delay the onset of type 2 diabetes when compared with placebo but with substantial gastrointestinal side effects.

Lifestyle intervention vs. placebo

- Two RCTs[6, 7] found that lifestyle interventions (diet and/or exercise) significantly reduced the incidence of diabetes in the intervention group when compared with the control group.
- Pan[6] enrolled 577 people without diabetes over the age of 25 who tested positive for glucose intolerance and followed them for six years.
- These participants were randomized to a control group, diet-only group, exercise-only group, or diet plus exercise group. The diet intervention differed based on individual BMI. Those with a BMI = 25 kg/m^2 were encouraged to reach a goal of 23 kg/m^2.
- The incidence of diabetes at the end of the six year follow-up was significantly greater in the control group than any of the intervention groups. The difference was even more statistically significant when the results were broken out by BMI ≥ 25 kg/m^2. The group that received the exercise intervention had the greatest difference from the control ($p < 0.01$) for individuals whose BMI was < 25 kg/m^2.
- Tuomilehto[7] recruited 522 middle-aged, overweight subjects with impaired glucose tolerance (IGT).
- Participants were randomized to oral and written information about diet and exercise or to individualized counseling aimed at reducing weight loss and increasing physical activity.
- At the end of four years, the incidence of diabetes was 23% in the control group and 11% in the treatment group (risk reduced by 58%; $p < 0.001$). There was also a statistically significant difference in favor of the intervention for weight loss and change in glucose intolerance.

Metformin vs. placebo

- One RCT found a significant difference in total incidence of diabetes in favor of metformin when compared with placebo.
- Li[8] conducted a small study (n = 70) that compared metformin (250 mg, three times daily) with placebo for 12 months in patients with impaired glucose tolerance.
- There was a statistically significant difference in total incidence of diabetes between groups ($p = 0.001$) in favor of metformin.
- Metformin was also found to significantly aid in reverting impaired glucose tolerance to back to normal ($p = 0.011$).

Lifestyle vs. metformin

- One RCT found that a lifestyle intervention reduced the development of diabetes to a greater extent than metformin treatment alone.
- The Diabetes Prevention Program[5] enrolled 3,234 patients age ≥ 25 from 27 centers nationwide with impaired glucose tolerance who were at high-risk for developing type 2 diabetes.
- Subjects were randomized to placebo plus information on diet and exercise, and intensive lifestyle changes with the aim of reducing weight by 7% through a low-fat diet and exercising for 150 minutes a week; or 850 mg metformin twice a day plus information on diet and exercise.
- The study was ended early due to the positive results of the interventions. The incidence of diabetes after three years was significantly less in the intervention groups than the control group. Risk of developing diabetes was reduced by 58% for the group that received intensive lifestyle changes and by 31% for the group receiving metformin.

Acarbose vs. placebo

- One RCT[9] found that patients with impaired glucose tolerance taking acarbose were less likely to develop diabetes when compared with placebo, even after adjustment for change in weight.
- The STOP-NIDDM Trial[9] enrolled 1,429 patients aged 54 years from nine centers worldwide with impaired glucose tolerance who were at high-risk for developing type 2 diabetes. Patients had a BMI between 25 to 40 kg/m^2.
- Subjects were given information on diet and exercise and a yearly visit with the dietitian they were then randomized to placebo or 100 mg (three times daily) of acarbose.
- At the end of three years the study showed that patients taking acarbose were 25% less likely to develop diabetes as compared with the control group (NNT = 11 to delay the onset of diabetes by 3.3 years).
- Weight loss contributed to the decreased risk of diabetes ($p < 0.00001$) but treatment with acarbose decreased the risk of diabetes even after adjustment for change in weight ($p = 0.0063$).
- The intervention also significantly increased the reversion of IGT to normal GT ($p < 0.0001$).
- Acarbose when compared with placebo resulted in more gastrointestinal side effects (flatulence, diarrhea, or abdominal cramps).

Orlistat plus lifestyle vs. placebo

- One retrospective meta-analysis[10] found that the addition of orlistat to a traditional regimen of diet and exercise significantly improved oral glucose tolerance and diminished the rate of progression to type 2 diabetes. However, no conclusions can be made about orlistat as an alternative to lifestyle therapy.
- Heymsfield enrolled 675 patients with impaired fasting glucose whose BMI ranged from 30 to 43 kg/m^2. Participants were randomized to (1) placebo plus a low-energy diet [30% of energy intake from fat; daily maintenance energy requirement (1.3 times calculated basal metabolic rate) minus 2,083 to 3,333 kJ/d (500 to 800 kcal/d)], or (2) orlistat 120 mg (three times daily) plus a low-energy diet. The mean length of follow-up was 582 days.
- Patients taking orlistat lost more weight (mean ±SEM, 6.72 ±0.41 kg from initial weight) than patients receiving placebo (3.79 ±0.38 kg; $p < 0.001$).
- A smaller percentage of subjects with impaired glucose tolerance at baseline progressed to diabetic status in the orlistat (3.0%) vs. placebo (7.6%) group.
- Among patients with IGT at baseline, glucose levels normalized in more participants after orlistat treatment (71.6% vs. 49.1%, $p < 0.04$).

Supporting Evidence from a Simulation Model

- "Archimedes" is the name of a very detailed, comprehensive, continuous simulation model of health care developed by the Biomathematics Unit of Kaiser Permanente's Care Management Institute. It can be used to explore the effects of a wide variety of health care interventions on health, logistic, and economic outcomes of major diseases in a complex health care system. The Archimedes model ran a simulation that was based on the inclusion criteria, treatment groups, and results of the Diabetes Prevention Program. The model has been validated and was built based on randomized, controlled trials. Since Archimedes has the ability to match and predict the results of UKPDS, it can be used to model the natural history of diabetes after it has been diagnosed and the effects of treatment.
- Archimedes expanded the number of people in each treatment group (n = 16,300) and extended the follow-up to ten years.
- At ten years, there was virtually no difference between the control group and the metformin group for myocardial infarctions (MIs). Lifestyle saved 94 MIs compared with control, but there was no difference between groups for CHD (coronary artery disease) death or life years.
- Thirteen cases of blindness, 56 cases of proteinuria, 66 foot ulcers, and 143 foot calluses were prevented by treatment compared with control.

Because of the limited effect of the interventions on health outcomes, and that the intervention only delays onset of diabetes by two to three years, caution is advised for *expensive* exercise and diet programs. The cost of the diabetes prevention program should be aligned with the value of the outcome.

Supporting Evidence from a Simulation Model

The cost-effectiveness analysis determined that lifestyle modification for high-risk people can result in cost-savings over 30 years if the annual cost of the intervention can be reduced to about $100. However, there was no evidence of the efficacy of such an intervention.[4]

2. Postpartum Screening for Diabetes in Women with a History of Gestational Diabetes Mellitus (GDM)

2 Screening for diabetes six weeks after delivery is recommended for women with gestational diabetes. *Consensus-based*

2009 Guideline

New evidence has been identified. Recommendations have been changed based on both new evidence and expert/consensus opinion.

Search Strategy

Studies reviewed included meta-analyses, systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. See Appendix B for more information on the search strategy.

Executive Summary

There is no direct evidence that screening for diabetes in women with a history of gestational diabetes prevents important health outcomes of interest such as development of type 2 diabetes and complications of diabetes. However, data regarding increased risk for diabetes in this population warrant review of indirect evidence. Based on population studies, the Agency for Healthcare Research and Quality (AHRQ) reports that gestational diabetes affects approximately 200,000 (7%) of the over 4 million births occurring annually in the United States, and it cites studies that indicate 15 to 60 percent of women with gestational diabetes will develop type 2 diabetes within 5 to 15 years of delivery.[11] These statements are supported by evidence identified by the research and review conducted for the KP National Diabetes Guideline in 2009. Bellamy et al. [12] concludes that in comparison to women with a history of normoglycemic pregnancy, women with a history of GDM have at least a 7-fold increased risk of developing type 2 diabetes (RR = 7.43, [95% CI: 4.79 to 11.51]). Given this established increased risk to develop type 2 diabetes, and the fact that treatment of diabetes can reduce the incidence of diabetes complications and CVD (See Problem Forumations 15 through 20), the Guideline Development Team (GDT) recommends that women with gestational diabetes be screened for diabetes six weeks after delivery.

Rationale:

A comprehensive systematic review of the literature identified one meta-analysis of 20 cohort studies that identified a seven-fold increased risk of developing type 2 diabetes following gestational diabetes (GDM), suggesting that scheduled postpartum screening for diabetes is warranted in women with a hyperglycemic pregnancy. Increased risk is also noted in a 2008 AHRQ report entitled *Therapeutic Management, Delivery, and Postpartum Risk Assessment and Screening in Gestational Diabetes*, cited below, as well as in a screening recommendation by the ADA.

Bellamy et al. [12] conducted a systematic review and meta-analysis of 20 cohort studies in which women with a history of GDM had developed type 2 diabetes at least six weeks after delivery, as confirmed by an oral glucose tolerance test or fasting plasma glucose concentration, or both. The control groups were women with a history of normoglycemic pregnancies. The study used a random-effects model for all analyses, using RevMan to calculate unadjusted summary relative risks with 95% CI. The 20 studies (N = 675,455), retrospective and prospective in design (see Table 1 for details); included 31,867 women with a history of GDM, with a total of 10,859 incident cases of type 2 diabetes. **In comparison to women with a history of normoglycemic pregnancy, women with a history of GDM had at least a 7-fold increased risk of developing type 2 diabetes (RR = 7.43 [95% CI: 4.79 to 11.51]).** Subgroup analysis was conducted to determine the source of heterogeneity in the overall effect estimate. Study characteristics, participant characteristics, and diagnostic criteria for GDM and type 2 diabetes (see Figure 4 for details) were noted; however, effect estimates were similar when studies were grouped according to those characteristics. Some heterogeneity was reduced when the largest study (n = 659,164 with 9502 cases of type 2 diabetes in women with GDM) was excluded; however, that study was considered of high methodologic value with large effect size. It was reported that 9/20 studies did not have participant drop-outs, and only 6 studies did not report on drop-out rates.

The authors were not able to identify the source of heterogeneity in the effect size, as they did not conduct individual-level meta-analysis with the available datasets. Studies that included women who developed late-onset type 1 diabetes were excluded. To account for potential publication bias in the 20 included studies, the authors provided a funnel plot highlighting that the smaller studies (< 100 case) garnered greater effect size than the larger studies (100 to 500 cases); however, the largest study garnered the highest number of cases (9,502 cases of type 2 diabetes). It is notable that the studies included were from 13 different countries, introducing a bias unique to clinical trial protocols in international settings, including but not limited to sample heterogeneity. It is also notable that studies spanned 30 years during which diagnostic criteria for type 2 diabetes were revised, and lowered at least once. Not only does that introduce a maturation threat to its internal validity, it may have lead to an underestimation of incidence reported. Regardless, this meta-analysis was conducted in a methodologically rigorous manner.

Table 1: Gestational Diabetes Mellitus (GDM) and Development of Type 2 Diabetes (T2DM)

	Study type, year, country	Ethnic origin	Mean maternal age (years; SD or 95% CI) of women with GDM/non-GDM	GDM criteria	Total women studied (degree of matching GDM/ non-GDM)	Mean follow-up (SD or 95% CI)	Definition of T2DM
Feig et al[18]	Retrospective cohort, 2008, Canada	Mixed	29·3 (5·5)	Canadian Institute for Health Information (discharge summary)[36]	659 164	5·2 years[i]	Ontario Diabetes Database[ii,37]
Lee H et al[15]	Prospective cohort[iii], 2008, Korea	Non-white	33·6 (4·8)	National Diabetes Data Group, 1979[iv,38]	1736[v] (248 IGT)	2·1 years[i]	Local[vi]
Madarász et al[21]	Retrospective cohort[iii], 2008, Hungary	White	33·1/30·0 (5·9)	WHO, 1999[vii,39]	107	3·6 years (GDM; 0·8)/ 8·1 years (non-GDM; 5·1)	WHO, 1999[vii,40]
Gunderson et al[22]	Prospective cohort, 2007, USA	Mixed	Matched range 18–30	Obstetric laboratory reports	2408	Total 20 year follow-up (72% followed for entire time)	American Diabetes Association, 1997[ix]/diabetes medication/self report
Vambergue et al[23]	Prospective cohort, 2007, France	Mixed	27·0 (5·2)/28·8 (5·8)	Carpenter and Coustan[x,41]	581[xi,xii] (175 AGT)	6·75 years (0·8)	American Diabetes Association, 1997[ix]
Lee A et al[24]	Retrospective cohort, 2007, Australia	Mixed	30·7 (5·1)/30·5 (4·6)	Australian Diabetes[xiii,42] (pregnancy guidelines)	6253[xiv]	2·2 years (GDM),[i] 8·6 years (non-GDM)[i]	WHO, 1998[vii,40]
Ferraz et al[17]	Prospective cohort, 2007, Brazil	Non-white	26·9/25·1	WHO, 1999[xv,43]	178[xvi]	6·2 years (0·8)	WHO, 1999[vii,40]
Krishnaveni et al[25]	Prospective cohort, 2007, India	Non-white	Matched age range	Carpenter and Coustan[x,41]	524	5 years	WHO, 1999[vii,40]
Morimitsu et al[26]	Prospective cohort, 2007, Brazil	Mixed	32/27 (7)	American Diabetes Association, 1997[xvii,14]	34[xviii]	16–24 weeks	American Diabetes Association, 1997[ix]
Järvelä et al[5]	Retrospective cohort[iii], 2006, Finland	White	31·6 (17·7–46·5)/31·3 (18·8–46·0)	Finnish Diabetes Association[xix,44]	870[vxii,xiv]	5·7 years (GDM; 1·0–11·6) 6·1 (non-GDM; 1·5–13·1)	Medication for T2DM linked to database[xx,45]
Albareda et al[27]	Prospective cohort, 2003, Spain	White	30·7/30·4	Second and third GDM workshop conference[xxi,46,47]	766[xv]	6·16 years (0·05–13·73)	WHO, 1998[vii,40]
Åberg et al[28]	Retrospective cohort, 2002, Sweden	White	Matched range 20–45	European Association for Study of Diabetes[xxii,48]	290	1 year	WHO, 1985[xxiii]
Linné et al[16]	Retrospective cohort[iii], 2002, Sweden	White	32·6/30·6	Local[xxiv]	80[vxiv,xxv]	15 years	Local[xxvi]
Bian et al[29]	Retrospective cohort, 2000, China	Non-white	29/29 (23–40)	National Diabetes Data Group, 1979[iv]	84[vxiv,xvii,xxvi]	5–11 years	WHO, 1985[xxiii]
Ko et al[30]	Prospective cohort, 1999, China	Non-white	34·0 (4·1)/34·4 (6·4)	Local[xxvii]	1232[v]	6 weeks	WHO, 1985[xxiii]
Osei et al[31]	Retrospective cohort, 1998, USA	Non-white	31·3 (2·0)/36·0 (0·9)	National Diabetes Data Group, 1979[iv]	65[xxix]	7 years	National Diabetes Data Group, 1979[xxx,49]
Damm et al[32]	Retrospective cohort, 1994, Denmark	White	30·1/26·7	Local[xxxi]	298[xv]	7·5 years[i]	WHO, 1985[xxiii]
Benjamin et al[33]	Retrospective cohort, 1993, New Mexico	Mixed	27·2/26·5	Local[xxxii,50]	94[vxii,xvi,xxxiii,51]	4·8 years (GDM)/ 5·5 years (non-GDM)	National Diabetes Data Group, 1979[xxx,49]
O'Sullivan[34]	Prospective cohort, 1991, USA	Mixed	..	Local[xxxii]	943	22–28 years	WHO, 1985[xxiii]
Persson et al[35]	Retrospective cohort, 1991, Sweden	White	31 (20–46)/30 (16–43)	WHO, 1985[xxxiv,51]	186[vxii,xix,xxxv]	3–4 years	WHO, 1985[xxiii]

AGT=abnormal glucose tolerance. FPG=fasting plasma glucose. IGT=impaired glucose tolerance. i=median values at follow-up only. ii=includes all individuals diagnosed with diabetes ≥90 days after delivery living within Ontario, Canada. iii=report is cited as a case-control study in the summary but as a cohort study in the methods. iv=two or more FPG concentrations ≥5·8 mmol/L or 1 h glucose ≥10·6 mmol/L, 2 h glucose ≥9·2 mmol/L, 3 h glucose ≥8·1 mmol/L after 100 g glucose load. v=matched by age. vi=FPG concentrations ≥7 mmol/L only. vii=FPG concentrations ≥7 mmol/L or 2 h glucose ≥11·1 mmol/L, or both, after 75 g oral glucose load. viii=FPG concentrations ≥7 mmol/L, or 2 h glucose ≥11·1 mmol/L after 75 g glucose load. ix=FPG concentrations ≥7 mmol/L or 2 h glucose ≥11·1 mmol/L, or both, after 75 g glucose load. x=FPG concentrations ≥5·3 mmol/L or 2 h plasma glucose ≥8·6 mmol/L, or 3 h glucose ≥7·7 mmol/L after 100 g oral glucose load. xi=matched by ethnic origin. xii=matched by parity. xiii=FPG concentrations ≥5·5 mmol/L or 2 h glucose ≥8·0 mmol/L after 75 g glucose load (before Jan 01, 1999, FPG ≥7·8 mmol/L, 1 h glucose ≥9 mmol/L and 2 h glucose ≥7·0 mmol/L after 50 g glucose load). xiv=matched by year of delivery. xv=FPG concentrations ≥7 mmol/L or 2 h glucose ≥11·1 mmol/L, or both, (group also included gestational impaired glucose tolerance=FPG <7 mmol/L and 2 h glucose 7·8–11·1 mmol/L) after 75 g oral glucose load. xvi=matched by body-mass index. xvii=two or more FPG concentrations ≥5·3 mmol/L, 1 h glucose ≥10·0 mmol/L, 2 h glucose ≥8·6 mmol/L, 3 h glucose ≥7·8 mmol/L after 100 g glucose load. xviii=matched by gestational age at study entry. xix=FPG concentrations ≥4·8 mmol/L or 1 h glucose ≥10·0 mmol/L, or 2 h glucose ≥8·7 mmol/L after 75 g oral glucose load. xx=medications obtained from central drug register with complete population coverage plus questionnaire. xxi=two or more FPG concentrations ≥5·8 mmol/L, 1 h glucose ≥10·6 mmol/L, 2 h glucose ≥9·2 mmol/L, 3 h glucose ≥8·1 mmol/L after glucose (75 g) load. xxii=FPG concentrations ≥6 mmol/L or 2 h glucose ≥9 mmol/L after 75 g glucose load. xxiii=FPG concentrations ≥7·8 mmol/L, or 2 h glucose ≥11·1 mmol/L after 75 g oral glucose load. xxiv=2 h glucose concentration ≥9 mmol/L after 75 g glucose load. xxv=matched by waist to hip ratio. xxvi=2 h glucose concentration >10 mmol/L after 75 g glucose load. xxvii=matched by social background. xxviii=two or more FPG concentrations ≥5·0 mmol/L or 1 h glucose ≥9·5 mmol/L, 2 h glucose ≥8·1 mmol/L, 3 h glucose ≥7·0 mmol/L after 50 g glucose load. xxix=study included a third group of 15 women who were not included in this meta-analysis. xxx=FPG concentrations ≥7·8 mmol/L or 2 h glucose 11·1 mmol/L after 75 g glucose load. xxxi=two or more venous plasma glucose concentrations >3 SD from the mean in women without gestational diabetes after 50 g glucose load (0 min: 6·4 mmol/L; 30 min: 10·1 mmol/L; 1 h: 10·1 mmol/L; 90 min: 8·7 mmol/L; 2 h: 7·6 mmol/L; 150 min: 7·6 mmol/L; 3 h: 6·6 mmol/L). xxxii=fasting venous whole blood glucose concentration ≥5 mmol/L or 2 h venous whole blood glucose ≥8·0 mmol/L or 3 h glucose ≥6·9 mmol/L) after 100 g glucose load. xxxiii=matched by length of follow-up. xxxiv=FPG concentrations ≥7 mmol/L and 2 h glucose ≥7·8 mmol/L after 75 g oral glucose load. xxxv=matched by prepregnancy weight and weight gain.

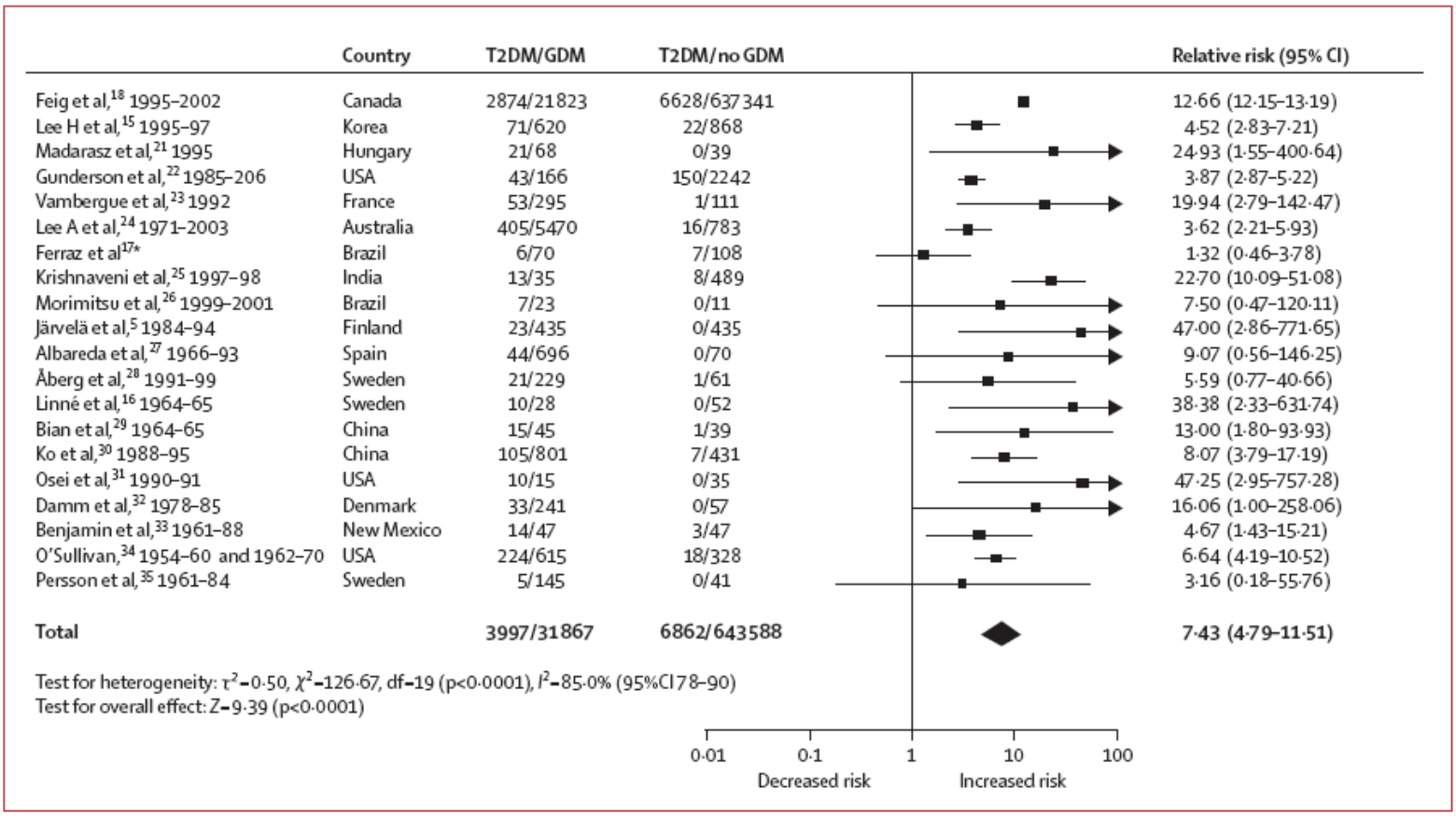

***Figure 2*: Risk of type 2 diabetes mellitus (T2DM) after gestational diabetes mellitus (GDM)**
x-axis is log scale. Each solid square represents a relative risk. Horizontal lines indicate 95% CIs. df=degrees of freedom. *Dates not available.

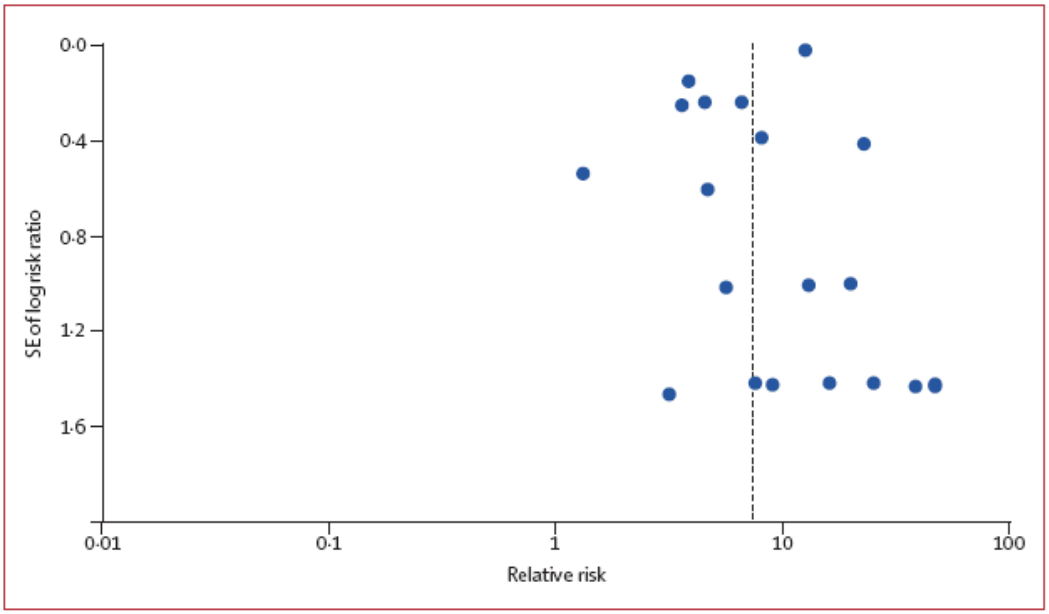

***Figure 3*: Funnel plot of 20 cohort studies included in meta-analysis**
x-axis is log scale. Dotted line is the summary relative risk (7·43).

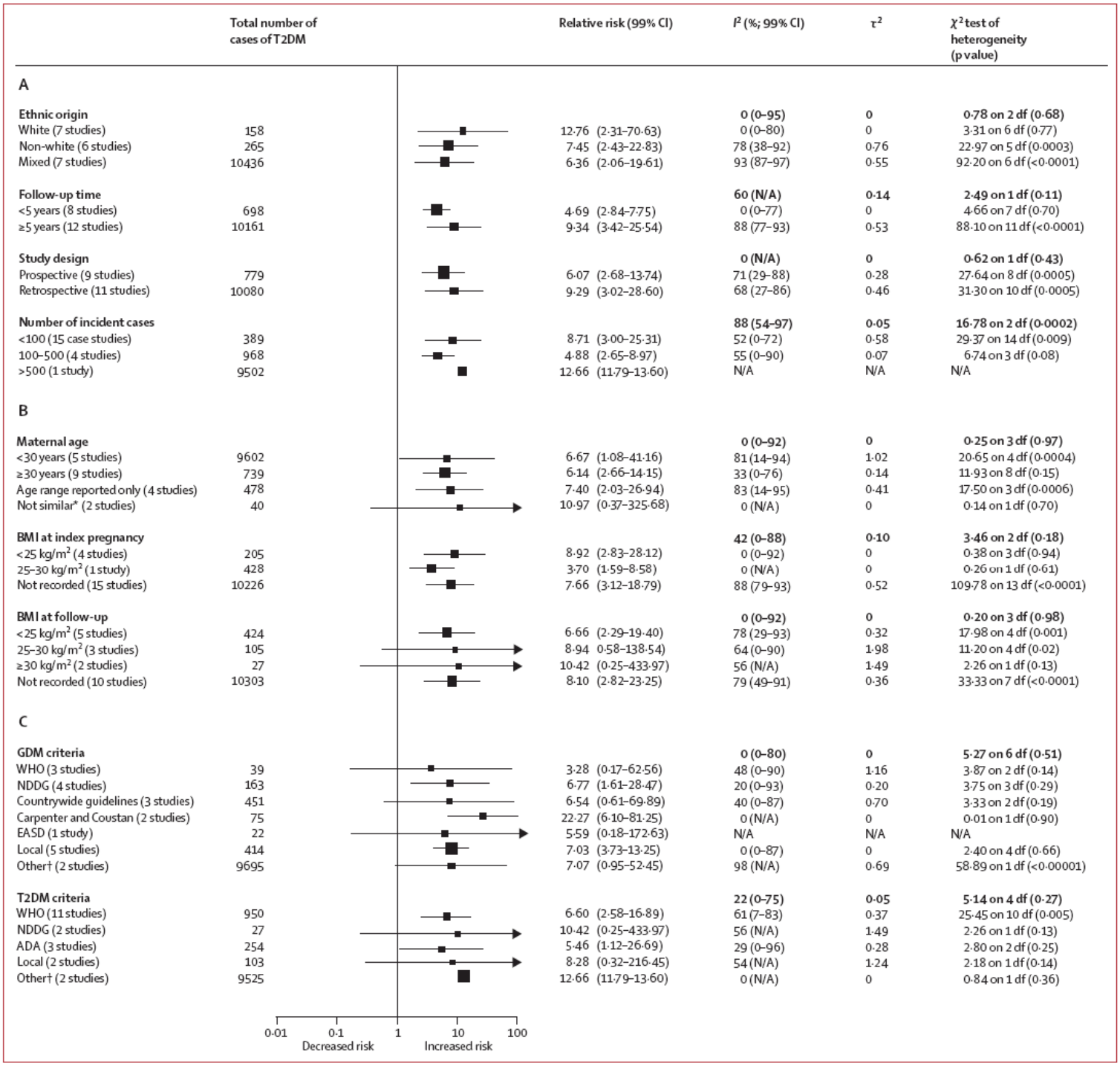

Figure 4: **Risk of type 2 diabetes mellitus (T2DM) grouped by study characteristics (A), participant characteristics (B), and diagnostic criteria (C)**
x-axis is log scale. Each solid square represents a relative risk. Horizontal lines indicate 99% CIs. ADA=American Diabetes Association. BMI=body-mass index. df=degrees of freedom. EASD=European Association for Study of Diabetes. GDM=gestational diabetes mellitus. N/A=heterogeneity not applicable because one study analysed. NDDG=National Diabetes Data Group. *Average ages of women with and without GDM were not similar; therefore effect of maternal age could not be assessed. †Includes databases and obstetric reports (table).

AHRQ 2008

An AHRQ Evidence Report entitled *Therapeutic Management, Delivery, and Postpartum Risk Assessment and Screening in Gestational Diabetes* contained two questions that focused on topics of interest here: "What risk factors are associated with the development of type 2 diabetes after gestational diabetes?" and, "What are the performance characteristics of diagnostic tests for type 2 diabetes in women with gestational diabetes?" The systematic review identified that anthropometric measures (i.e., weight, BMI, waist circumference), fasting blood glucose (FBG), and 2-hour glucose value are the strongest risk factors associated with development of type 2 diabetes following incidence of gestational diabetes. It did not find sufficient evidence to confirm that FBG out-performs the 75-gm OGTT in diagnosing type 2 diabetes after delivery of index hyperglycemic pregnancy.

Below is a summary of AHRQ's findings for each clinical question, presented verbatim. Further details, including evidence tables, are found in Appendix B.

Excerpt begins here.

Key Question 3

"What risk factors, including but not limited to family history, physical activity, pre-pregnancy weight, and gestational weight gain, are associated with short-term and long-term development of type 2 diabetes following a pregnancy with gestational diabetes?

Several factors were associated with the development of type 2 diabetes in women with previous gestational diabetes. Anthropometric measures before, during, and after pregnancy were found to be positively associated with the development of type 2 diabetes in 10 of 11 cohort studies. Waist circumference and BMI were the strongest anthropometric measures associated with type 2 diabetes in gestational diabetic women. Early gestational age at diagnosis of gestational diabetes (primarily less than 24 weeks) and use of insulin versus diet for glucose control were key pregnancy-related clinical factors that were positively associated with type 2 diabetes. Physiologic measures, including FBG and 2-hr plasma glucose levels during the diagnostic OGTT, were also associated with development of type 2 diabetes. Higher blood glucose following a screening 50-gm GCT, prior gestational diabetes, and OGTT area under the curve during both the antepartum and postpartum periods were positively associated with development of type 2 diabetes, but the strength of the associations was not consistent across studies. There is conflicting data on progesterone-only contraceptive use and the risk for developing type 2 diabetes. Elevated postpartum homocysteine levels were positively associated with type 2 diabetes in one study. Surprisingly, there were no studies of lifestyle factors in women with gestational diabetes that met our review criteria.

After a review of the available evidence, we concluded that the strongest epidemiological risk factors were anthropometric measures prior to pregnancy and during both the antepartum and postpartum periods. Taking into consideration the quantity, quality, and consistency of the studies evaluating the association of risk factors for type 2 diabetes following a pregnancy with gestational diabetes, we graded the strength of the evidence as very low. While there was substantial consistency in the direction of association across studies for many of the risk factors, there was considerable variation in the covariates adjusted for in multivariate models across studies.

Key Question 4

"What are the performance characteristics (sensitivity, specificity, and reproducibility) of tests for diagnosing type 2 diabetes after pregnancy in patients with a history of gestational diabetes? Are there differences in the performance characteristics of the test results based on subgroup analysis?

Several studies have pointed to poor physician compliance with postpartum glucose screening for type 2 diabetes among women with a history of gestational diabetes. We reviewed the available studies of the diagnostic accuracy of screening for type 2 diabetes in this population. We identified 8 studies and 10 evaluations of screening tests, with three types of comparisons:

Two different diagnostic fasting value thresholds applied to the 75-gm OGTT (the WHO 1985 criteria compared to the WHO 1999 criteria);

Single FBG level greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) compared to the 75-gm OGTT (WHO 1999); and

Single FBG greater than 7.0 mmol/L (126 mg/dL) (ADA 1997) compared to the 75-gm OGTT (WHO 1985).

For the first comparison, we concluded that there was acceptable specificity (98 percent) for the OGTT using either a FBG value greater than 7.0 mmol/L (126 mg/dL) or greater than 7.8 mmol/L (140 mg/dL). For the second comparison, we were unable to draw meaningful conclusions. The sensitivities for a single FBG greater than 7.0 mmol/L (126 mg/dL), as compared to a complete OGTT using the same FBG threshold, ranged from 46 to 89 percent in the three studies. For the third comparison, there were five studies, which reported a high specificity of the FBG greater than 7.0 mmol/L (126 mg/dL). However, there was a wide range of sensitivity, from 14 to 100 percent.

The six studies that used an FBG threshold greater than 7.8 mmol/L (140 mg/dL) in the reference test may be obsolete, since current guidelines recommend an FBG greater than 7.0 mmol/L (126mg/dL). The wide variation in the reported sensitivities for studies that compared the OGTT as the reference test to a single FBG greater than 7.0 mmol/L (126 mg/dL) may reflect differences in the study samples' risk for type 2 diabetes, based on heterogeneity of study design and population. The overall strength of evidence was very low because of the high loss-to-follow-up rates (22 to 82 percent) for studies using clinic convenience samples.

Excerpt ends here.

Supplemental Information

*American Diabetes Association: Standards of Medical Care in Diabetes—2009**

Excerpt begins here.

> **Recommendation:** Women with GDM should be screened for diabetes six to 12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or prediabetes. (Evidence Grade E: Expert Consensus or Clinical Experience)
>
> **Rationale:** Because women with a history of GDM have a greatly increased subsequent risk for diabetes, they should be screened for diabetes six to 12 weeks postpartum, using nonpregnant OGTT criteria, and should be followed up with subsequent screening for the development of diabetes or prediabetes. For information on the National Diabetes Education Program (NDEP) campaign to prevent type 2 diabetes in women with GDM, go to www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf.

Excerpt ends here.

2007 Guideline:

For the 2007 update, no new evidence was found, the recommendation remains unchanged from the 2005 guideline.

Approximately 2 to 5% of all non-diabetic pregnant women develop gestational diabetes. Although gestational diabetes usually resolves itself after pregnancy, women with a history of GDM are at higher risk for developing type 2 diabetes.

One case-control study[13] followed 28 women with GDM for 15 years and found that ten women (35%) of the GDM group were diagnosed with type 2 diabetes compared with none in the control group. Fifty-four percent of the GDM women stated that they had never been informed that they had a higher risk of developing type 2 diabetes mellitus than others.

Based on the high-risk for GDM women to develop type 2 diabetes and strong evidence supporting lifestyle changes and weight control to reduce the development of type 2 diabetes,[5, 14] the GDT recommends that postpartum GDM patients be counseled on the higher risk of developing type 2 diabetes and the preventative effects of lifestyle changes and weight control.

* For an explanation of the letter grading in this excerpt, please see Appendix C.

3. PostPartum Follow-Up of Gestational Diabetes Mellitus

3A Information/education about the increased risk of developing type 2 diabetes following gestational diabetes is recommended for women with gestational diabetes. *Consensus-based*

3B For women with recent gestational diabetes, long-term postpartum follow-up, including advice on diet, exercise and behavior modification, is recommended to prevent future progression to type 2 diabetes. *Consensus-based*

2009 Update

New evidence has been identified. Recommendations have been changed based on both new evidence and expert/consensus opinion.

Search Strategy

Studies reviewed included meta-analyses, systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. See Appendix B for more information on the search strategy.

Executive Summary

There is no high-quality direct evidence that therapeutic intervention for diabetes in women with a history of gestational diabetes prevents important health outcomes of interest such as prevention of diabetes and prevention of complications of diabetes. However, the identification of risk factors for the development of diabetes in women with a history of gestational diabetes in an Agency for Healthcare Research and Quality (AHRQ) report warrants inclusion here.[11] The AHRQ reports that waist circumference and BMI were the strongest anthropometric measures associated with type 2 diabetes in gestational diabetic women.[11] A low-quality subgroup analysis[15]of women with a history of GDM in the large Diabetes Prevention Program study[16] suggested that lifestyle therapy such as diet, exercise and behavioral change, as well as metformin, yielded statistically significant risk reductions in developing diabetes, compared to placebo. Given the established increased risk of developing type 2 diabetes in women with a history of GDM, the GDT recommends that women with gestational diabetes be advised on the increased post-partum risk of type 2 diabetes and the preventive effects of diet, exercise, and behavior change after delivery.

Rationale:

A comprehensive systematic review of the literature identified one low-quality RCT that reviewed the effect of intensive lifestyle therapy and metformin on preventing type 2 diabetes in those with gestational diabetes.

The Diabetes Prevention Program study[16] identified a statistically significant 58% reduction in incidence for those treated with lifestyle therapy (a 16-lesson curriculum covering diet, exercise and behavior modification) in comparison to placebo; and a statistically significant 31% incidence reduction for those treated with 850 mg metformin take once a day in comparison to placebo. Furthermore, the reduction in incidence of diabetes was statistically significantly greater in the lifestyle therapy group, than the metformin group. Ratner's subgroup analysis of those with previous GDM identified that lifestyle therapy yielded a 53% reduction in risk to develop diabetes in comparison to placebo ($p = 0.002$); and, metformin yielded a 50% reduction in risk to develop diabetes in comparison to placebo ($p = 0.006$).

Ratner et al. [15] reports on a cohort of women (N = 350), with a history of GDM, as well as a cohort of women without a history of GDM, enrolled in the large Diabetes Prevention Program RCT with a mean 12-year interval since delivery of their first GDM pregnancy. This review will only highlight study findings on women with a history of GDM. Women with a history of GDM, average age 43.0 ±7.6, were randomized (blinding not addressed) to a placebo group (n = 122), a metformin therapy group (dosage and regimen not reported) (n = 111); and, to an intensive lifestyle (ILS) group (i.e., exercise, time and intervals not reported) (n = 117). The study reported that among women with GDM, metformin yielded a 50% reduction in risk to develop diabetes in comparison to placebo (p = 0.006) (no crude data provided). ILS yielded a 53% reduction in risk to develop diabetes in comparison to placebo (p = 0.002) (no crude data reported). Observed hazard rates were also reported for this cohort. Incidence of diabetes (number cases per 100-person years (adjusted for age)) was 7.8 in the metformin group, 7.4 in the ILS group, and 15.2 in the placebo group. The authors conclude that intervention with metformin and ILS are comparable in their effect on preventing diabetes in women with a history of GDM, with an estimated five to six women requiring treatment to prevent one case of diabetes over three years. Several methodological shortcomings compromise the value of this study's findings. This study was a post-hoc analysis of a larger study the randomization of which was not stratified by GDM. As such, it suffers from selection bias. The GDM sample is not generalizable due to the advanced maternal age included (43 ±7.6 for those with history of GDM; 51.5 ±9.7 for those without a history of GDM). The mean 12-year interval since delivery of the first GM pregnancy poses the threat of maturation to its internal validity. In addition, it did not provide details regarding the administration of the treatments (metformin, ILS). Furthermore, this study did not provide actual numbers for its results but only provided the percentage of risk reduction, preventing statistical verification of the outcomes.

Despite the shortcoming of these studies, the GDT makes a consensus-based recommendation that women with gestational diabetes be advised on the increased post-partum risk of type 2 diabetes and the preventive effects of diet, exercise, and behavior change after delivery.

AHRQ 2008

An AHRQ Evidence Report entitled *Therapeutic Management, Delivery, and Postpartum Risk Assessment and Screening in Gestational Diabetes* contained one question that focused on topics of interest here: "What risk factors are associated with the development of type 2 diabetes after gestational diabetes?" The systematic review identified that anthropometric measures (i.e., weight, BMI, waist circumference), fasting blood glucose (FBG), and 2-hour glucose value are the strongest risk factors associated with development of type 2 diabetes following incidence of gestational diabetes.

Below is a summary of AHRQ's findings for each clinical question, presented verbatim. Further details, including evidence tables, are found in Appendix B.

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Excerpt ends here.

2007 Guideline:

For the 2007 update, no new evidence was found; the recommendation remains unchanged from the 2005 guideline.

Based on the high-risk for women with GDM to develop type 2 diabetes and strong evidence supporting lifestyle changes and weight control to reduce the development of type 2 diabetes,[5, 14] the GDT recommends that postpartum GDM patients be counseled on the higher risk of developing type 2 diabetes and the preventative effects of lifestyle changes and weight control.

Screening

4. Screening for Type 2 Diabetes

4A Screening is recommended for asymptomatic adults with sustained blood pressure > 135/80 mmHg (either treated or untreated) to establish an appropriate blood glucose target. *Evidence-based: B*

4B Screening is an option for all other adults with risk factors for diabetes.

- Age 45 years or older
- Under age 45 and overweight (BMI ≥ 25kg/m^2, may be lower in some ethnic groups) with additional risk factors:
  - physical inactivity,
  - first-degree relative with diabetes,
  - members of a high-risk ethnic population (e.g., Black/African American, Latino, Native American, Asian American, Pacific Islander),
  - women who delivered a baby weighing > 9 lb or were diagnosed with GDM,
  - hypertension (≥ 140/90 mmHg or on therapy for hypertension),
  - HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l),
  - women with polycystic ovarian syndrome (PCOS),
  - A1C ≥ 5.7%, IGT or IFG on previous testing,
  - other clinical conditions associated with insulin resistance (e.g., severe obesity [defined as BMI ≥ 40], acanthosis nigricans), and/or
  - history of cardiovascular disease

Consensus-based

4C In the absence of sufficient evidence to recommend an optimal screening frequency, regions are encouraged to set appropriate screening intervals. *Consensus-based*

Evidence Grade*

Evidence for Recommendation 4A: Fair

* The criteria for grading the strength of the evidence as either "good," "fair," or "insufficient" adheres to the KP National Guideline Program's "Policies and Procedures" documents entitled "Label and Language of Recommendations" and "KP System for Grading the Strength of a Body of Evidence," which are located in Appendix A.

2009 Update:

New indirect evidence has been identified. Recommendations have been changed based on both new evidence and expert/consensus opinion.

Search Strategy

Studies reviewed included meta-analyses, systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. See Appendix B for more information on the search strategy.

Executive Summary

A systematic review conducted by the USPSTF in 2003 and updated in 2008, and an update of the KP National Diabetes Guideline in 2009, did not find studies that included screen-detected asymptomatic patients in order to assess the direct link between screening and positive health outcomes. There is also no evidence that screening people with increased risk for diabetes (including but not limited to those with impaired fasting glucose (IFG)) results in benefit in important health outcomes. However, the GDT made a consensus-based decision to adopt a modified version of the recommendation by the American Diabetes Association (ADA) to test for diabetes in asymptomatic adults that have specific risk factors, because it agrees with the ADA that "both conditions are common, increasing in prevalence, and impose significant public health burdens," and, because these risk factors are supported by findings of the prediction model tested in the Framingham Offspring Study.[17] The GDT also adopted the USPSTF recommendation to screen those with blood pressure >135/80 mmHg so that an appropriate blood pressure target is determined which is based on fair evidence that "persons with hypertension and type 2 diabetes benefit from lower blood pressure targets than persons with hypertension but without diabetes."

Rationale:

No new evidence directly addressing the clinical question was identified. A clinical guideline from the USPSTF, with an updated evidence review from the AHRQ, originally issued in 2003, and updated in 2008, is considered the primary source of evidence here. The USPSTF states that there is insufficient evidence for a screening recommendation for the general population (asymptomatic persons) with some benefit apparent for screening those with hypertension (as noted in the recommendations above). A recommendation from the ADA supported by fair evidence, and three studies stating increased risk for specific populations are summarized below in the Supplemental Information section.

Screening Adults for Type 2 Diabetes: A Review of the Evidence for the U.S. Preventive Services Task Force (2008)

Excerpt begins here.

No direct evidence clearly determines whether screening asymptomatic individuals for diabetes or prediabetes alters health outcomes (USPSTF Table 1 below). Evidence shows that persons with diabetes benefit from control of blood pressure and lipid levels, but studies have not included persons with screening-detected diabetes. Persons with hypertension and type 2 diabetes benefit from lower blood pressure targets than persons with hypertension but without diabetes. Persons with newly diagnosed, largely clinically detected, diabetes benefit from intensive glycemic control, largely because of a reduction in microvascular events. Evidence shows that intensive lifestyle modification in persons with prediabetes—an implicitly screening-detected population—delays the progression to clinical diabetes, but whether treatment alters final health outcomes is unknown because studies were not powered for those outcomes or were not of sufficient duration.

USPSTF Table 2 and USPSTF Table 3 show the numbers needed to screen to prevent an outcome of interest in different theoretical populations. These outcomes have not changed from the estimates of the previous USPSTF review because we identified no new data on the effectiveness of these interventions. As noted elsewhere, interventions that target cardiovascular events produce greater effects than those that target microvascular complications occurring later in the disease process.

Based on the DPP and the Finnish Diabetes Prevention Study, screening 1000 persons with prediabetes will delay 44 cases of type 2 diabetes over 3.0 years. Pharmacotherapy with metformin (based on DPP data) produced a somewhat less favorable number needed to screen. Many important assumptions underlying number-needed-to-screen estimates remain, including length of the asymptomatic period, prevalence of undiagnosed diabetes or prediabetes, incidence rates of diabetes complications, and treatment effect.

Screening targeted to populations at risk for diabetes would probably increase the yield and economic efficiency of screening, and risk scores have been developed to identify those at high risk for diabetes. In the DPP, older age and higher body mass index increased the yield of screening across ethnic groups. On the other hand, the prevalence of diagnosed diabetes in certain high-risk groups, such as non-Hispanic black/African American persons and Mexican-American persons, has increased, whereas the proportion of persons with undiagnosed disease in those groups has decreased, suggesting that opportunistic screening targeted to populations at high risk may already be occurring. This trend reduces the prevalence of undiagnosed diabetes and increases the number needed to screen to prevent adverse events in the remaining unscreened group.

A diabetes population of significant interest to a screening program would be individuals who would benefit from aggressive interventions to reduce macrovascular complications in persons who would not have been otherwise identified through recommended hypertension and hyperlipidemia screening. Many persons with diabetes are hypertensive or have additional cardiovascular disease risk factors, and those with the highest cardiovascular risk profiles are likely to benefit most from treatment. As shown in the Heart Protection Study, elevated low-density lipoprotein cholesterol levels alone may not identify many persons with diabetes and dyslipidemia who might benefit from lipid-lowering treatment, but this population had higher-than-average cardiovascular risk profiles. The benefit of identifying and treating asymptomatic diabetes in normotensive, non-dyslipidemic persons at average cardiovascular risk is unclear.

The potential yield of diabetes and prediabetes screening must be weighed carefully against the potential harms of screening and diagnosis. We did not identify evidence suggesting serious adverse effects of screening for type 2 diabetes. The literature does, however, have important limitations. Included studies examined persons at high risk for diabetes, and thus the results may not be applicable to mass screening programs that are not targeted. Theoretical concerns include the effects of labeling on anxiety and insurability, but available evidence is insufficient to support or refute these concerns.

Several limitations deserve mention. First, we restricted our review of diabetes treatment to studies with mean diabetes duration of one year or less, because we felt that these patient populations would most closely resemble screening-detected populations. Individuals with longstanding type 2 diabetes will likely show greater benefits from treatment, so focusing on treatment of early disease, in the absence of trials with extended follow-up, may underestimate the effectiveness of treatment and therefore screening interventions. For studies comparing a given treatment among persons with and persons without type 2 diabetes, we included studies of any duration of disease, and the applicability of these data to populations with screening-detected disease is uncertain. Second, attempts to divide patients with diagnosed diabetes into those with a "clinical diagnosis" based on symptoms and those deemed to be "screened" because of alleged asymptomatic status does not truly compare "not screened" with "screened" patients. Third, participants with prediabetes in studies of intensive lifestyle interventions may not be representative of general prediabetic populations. For example, the level of physical inactivity in the DPP cohort was less than that reported in the Third National Health and Nutrition Examination Survey.

Fourth, most of the data on diabetes treatment were from pre-specified subgroup analyses of large trials that included both diabetic and non-diabetic populations. The diabetes and non-diabetes subgroups had important differences, and subgroup analyses were often underpowered to demonstrate significant changes in primary outcomes. Prevention trials among persons with prediabetes were powered to examine the primary outcome of new cases of diabetes and not to examine long-term health outcomes, such as cardiovascular events.

Models rely on data from trials and observational studies and are only as good as the data and assumptions underlying them. All seven models that we identified that examined the effect of screening interventions lack transparency to some degree, and all have had one or more of their important underlying assumptions criticized.

Further research is needed to define the benefits and harms of screening average-risk individuals for type 2 diabetes. We must learn whether early, aggressive glycemic control in persons with diabetes produces improvements in clinical outcomes after many years of follow-up. An extension of the largest study of an initial strategy of sustained tight glycemic control in type 1 diabetes suggested that participants originally randomly assigned to tight glycemic control had a significant reduction in cardiovascular events at long-term follow-up despite similar glycemic control in the control group during the post-randomization period. To date, similar data are unavailable for type 2 diabetes. We also need studies to define the duration of the prediabetes phase and identify measurable risk factors for progression to diabetes and its complications, particularly cardiovascular disease.

The cost-effectiveness of diabetes screening programs is considered to be mainly determined by the long-term health benefits rather than the cost of detection and treatment of diabetes. Thus, intervention research needs to continue focusing on long-term, sustainable interventions that affect health outcomes in real-world settings. Further work is also needed to examine the effect of screening and diagnosis on patient self-efficacy, motivation for lifestyle change, and the potential psychological effects of labeling.

Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence fails to demonstrate health benefits for screening general populations or persons at high risk for diabetes complications without hypertension. Persons with hypertension do benefit from knowing their diagnosis of diabetes, because blood pressure targets are lower than for non-diabetic persons. Although intensive lifestyle interventions delay or prevent diabetes onset in persons with prediabetes, positive effects of this delay on long-term health outcomes have not been adequately demonstrated.

Excerpt ends here.

AHRQ's Screening Adults for Type 2 Diabetes Update of 2003 Systematic Evidence Review for the U.S. Preventive Services Task Force

An update of the USPSTF statement previously cited in this guideline was updated by AHRQ in June of 2008. AHRQ conducted systematic reviews to answer the clinical questions listed below, followed by a summary of findings.

Excerpt begins here.

> **Key Question 1** *Is there direct evidence that systematic screening for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance among asymptomatic adults improves health outcomes?*
>
> **Key Question 2** *Does beginning treatment of type 2 diabetes early as a result of screening provide an incremental benefit in health outcomes compared with initiating treatment after clinical diagnosis?*
>
> **Key Question 3** *Does beginning treatment of impaired fasting glucose or impaired glucose tolerance early as a result of screening provide an incremental benefit in final health outcomes compared with initiating treatment after clinical diagnosis of type 2 diabetes?*
>
> **Key Question 4** *What adverse effects result from screening a person for type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance?*
>
> **Key Question 5** *What adverse effects result from treating a person with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance detected by screening?*
>
> **Results**: There were no RCTs examining the effectiveness of a DM2 screening program. A small, case-control study did not suggest a benefit from screening when microvascular complications were considered. No study directly compared treatment effects between screen-detected and clinically detected diabetic persons, nor have studies to date reported treatment effects in a screening-detected cohort with diabetes. Modeling studies suggest that screening for DM2 may be relatively cost-effective when macrovascular benefits of optimal blood pressure control are taken into account.
>
> There was no clear evidence that persons with DM2 detected by screening would respond differently to specific antihypertensive regimens compared to persons without diabetes, and persons with diabetes and no known cardiovascular disease benefit from aggressive lipid control to a similar extent as persons without diabetes, but with known cardiovascular disease. In two new studies, aspirin did not appear to reduce the risk of myocardial infarction in DM2, but may lower the risk of ischemic stroke in women. There were no new data examining glycemic control strategies in persons with newly diagnosed DM2.

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

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

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

Excerpt ends here.

Supplemental Information

*American Diabetes Association: Standards of Medical Care in Diabetes—2009**

Excerpt begins here.

Recommendation: Testing for Prediabetes and Diabetes in Asymptomatic Patients
Testing to detect prediabetes and type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥ 25 kg/m^2) and who have one or more additional risk factors† for diabetes. In those without these risk factors, testing should begin at age 45 years. (B)

- If tests are normal, repeat testing should be carried out at least at 3-year intervals. (E)
- To test for prediabetes or diabetes, an FPG test or 2-h OGTT (75-g glucose load) or both are appropriate. (B)
- An OGTT may be considered in patients with impaired fasting glucose (IFG) to better define the risk of diabetes. (E)
- In those identified with prediabetes, identify and, if appropriate, treat other cardiovascular disease (CVD) risk factors. (B)

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Although the effectiveness of early identification of prediabetes and diabetes through mass testing of asymptomatic individuals has not been definitively proven (and rigorous trials to provide such proof are unlikely to occur), prediabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, increasing in prevalence, and impose significant public health burdens. There is a long pre-symptomatic phase before the diagnosis of type 2 diabetes is usually made. Relatively simple tests are available to detect preclinical disease. Additionally, the duration of glycemic burden is a strong predictor of adverse outcomes, and effective interventions exist to prevent progression of prediabetes to diabetes and to reduce risk of complications of diabetes.

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* See Appendix C for an explanation of the ADA grading.

† ADA lists the following as risk factors for pre-diabetes and diabetes: overweight (BMI ≥ 25 kg/m^2); physical inactivity; first-degree relative with diabetes; members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander); women who delivered a baby weighing > 9 lb or were diagnosed with GDM; hypertension (≥ 140/90 mmHg or on therapy for hypertension); HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l); women with polycystic ovarian syndrome (PCOS); IGT or IFG on previous testing; other clinical conditions; associated with insulin resistance (e.g., severe obesity, acanthosis nigricans); history of CVD.

Recommendations for testing for prediabetes and diabetes in asymptomatic, undiagnosed adults are listed in the footnote† below [*sic*]. Testing should be considered in adults of any age with BMI ≥ 25 kg/m^2 and one or more risk factors for diabetes. Because age is a major risk factor for diabetes, testing of those without other risk factors should begin no later than age 45 years.

Either FPG testing or the 2-h OGTT is appropriate for testing. The 2-h OGTT identifies people with either IFG or IGT, and thus, more pre- to diabetic people at increased risk for the development of diabetes and CVD. It should be noted that the two tests do not necessarily detect the same pre- to diabetic individuals. The efficacy of interventions for primary prevention of type 2 diabetes has primarily been demonstrated among individuals with IGT, not individuals with IFG (who do not also have IGT). The FPG test is more convenient, more reproducible, less costly, and easier to administer than the 2-h OGTT. An OGTT may be useful in patients with IFG to better define the risk of diabetes.

The appropriate interval between tests is not known. The rationale for the three-year interval is that false-negatives will be repeated before substantial time elapses, and there is little likelihood that an individual will develop significant complications of diabetes within three years of a negative test result.

Because of the need for follow-up and discussion of abnormal results, testing should be carried out within the health care setting. Community screening outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Conversely, there may be failure to ensure appropriate repeat testing for individuals who test negative. Community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed.

Excerpt ends here.

† ADA lists the following as risk factors for pre-diabetes and diabetes: overweight (BMI ≥ 25 kg/m^2); physical inactivity; first-degree relative with diabetes; members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander); women who delivered a baby weighing > 9 lb or were diagnosed with GDM; hypertension (≥ 140/90 mmHg or on therapy for hypertension); HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l); women with polycystic ovarian syndrome (PCOS); IGT or IFG on previous testing; other clinical conditions; associated with insulin resistance (e.g., severe obesity, acanthosis nigricans); history of CVD.

The following studies were identified in the updated search. They provide low-quality evidence regarding the risk of developing diabetes in specific populations. The relative risks for the risk factors of Hepatitis C or use of antipsychotics do not meet a ≥ 2 threshold to warrant an evidence-based screening recommendation. Brief descriptions of these studies are provided as supplemental information.

- **Hepatitis C Virus (HCV):** White et al.[18] reviewed 34 studies (N = N/A) to examine increase risk of diabetes in those infected with HCV compared to those without HCV. The pooled risk estimate from 15 retrospective studies is OR = 1.68 (95% CI: 1.15 to 2.20). The pooled hazard ratio from 3 prospective studies is HR = 1.67 (95% CI: 1.20 to 1.40).
- **Antipsychotics:** Smith et al.[19] reported on a poor quality meta-analysis of 11 studies (N not reported) comparing the risk of having or developing diabetes while on second generation anti-psychotics with first-generation anti-psychotics in people with schizophrenia or related disorders. It identified an overall relative risk of a diagnosis of diabetes in those prescribed second-generation anti-psychotics of 1.32 [95% CI: 1.15 to 1.51] compared to those prescribed first-generation anti-psychotics.
- **Middle-Aged Adults:** The Framingham Offspring Study[17] tested three diabetes-predicting models in a 99% white, non-hispanic, middle aged (mean age: 54) population (N = 3140) for an average of 7 years. It conducted multivariate prediction according to personal variables (e.g., age, sex, BMI, parental history, etc.); simple clinical variables (e.g., blood pressure, triglyceride level, waist circumference, etc.); and, complex clinical variables (e.g. fasting glucose level, 2-hour OGTT, C-reactive protein level, etc.). Parental history of diabetes, obesity, hypertension, low levels of high-density lipoprotein cholesterol, elevated triglyceride levels, and impaired fasting glucose findings but not large waist circumference (AROC 0.85) were identified as statistically significant predictors of type 2 diabetes.

Table 2. Multivariate Prediction of T2DM According to Personal Variables

Variable	OR (95% CI)	*P* Value
Age, y		
<50	1 [Reference]	
50-64	1.54 (1.04-2.27)	.03
≥65	1.74 (1.06-2.85)	.03
Male	1.25 (0.89-1.74)	.20
Parental history of diabetes	1.87 (1.28-2.72)	.001
BMI		
<25.0	1 [Reference]	
25.0-29.9	2.35 (1.39-3.96)	.001
≥30.0	6.41 (3.85-10.65)	<.001
Intercept	–4.499	
AROC	0.724	

Abbreviations: AROC, area under the receiver operating characteristic curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Source: Wilson 2007

Table 3. Multivariate Prediction of T2DM According to Simple Clinical Variables

Variable	Simple Clinical Model					
	Obesity by BMI Only		Obesity by Waist Circumference Only		Obesity by BMI and Waist Circumference	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y						
<50	1 [Reference]		1 [Reference]		1 [Reference]	
50-64	0.98 (0.64-1.50)	.93	0.94 (0.62-1.44)	.79	0.98 (0.64-1.50)	.90
≥65	0.92 (0.54-1.59)	.77	0.83 (0.49-1.43)	.51	0.91 (0.53-1.56)	.70
Male	0.99 (0.70-1.41)	.95	1.09 (0.77-1.54)	.65	1.05 (0.73-1.50)	.80
Parental history of diabetes mellitus	1.76 (1.17-2.64)	.006	1.75 (1.17-2.61)	.007	1.78 (1.19-2.67)	.005
BMI						
<25.0	1 [Reference]		Not included		1 [Reference]	
25.0-29.9	1.35 (0.78-2.34)	.28	Not included		1.21 (0.68-2.14)	.50
≥30.0	2.50 (1.45-4.30)	.001	Not included		1.86 (0.94-3.67)	.07
Blood pressure >130/85 mm Hg or receiving therapy	1.65 (1.10-2.46)	.02	1.73 (1.16-2.59)	.007	1.62 (1.08-2.43)	.02
HDL-C level <40 mg/dL in men or <50 mg/dL in women	2.57 (1.75-3.77)	<.001	2.62 (1.79-3.84)	<.001	2.55 (1.74-3.74)	<.001
Triglyceride level ≥150 mg/dL	1.78 (1.22-2.59)	.003	1.78 (1.23-2.59)	.002	1.75 (1.20-2.56)	.004
Waist circumference >102 cm in men or >88 cm in women	Not included		1.98 (1.37-2.84)	<.001	1.42 (0.88-2.29)	.20
Fasting glucose level 100-126 mg/dL	7.25 (4.89-10.74)	<.001	7.17 (4.86-10.58)	<.001	7.16 (4.83-10.61)	<.001
Intercept	−5.517		−5.434		−5.363	
AROC	0.852		0.850		0.852	

Abbreviations: AROC, area under the receiver operating characteristic curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; T2DM, type 2 diabetes mellitus.
SI conversion factors: To convert HDL-C to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113.

Source: Wilson 2007

Table 5. Multivariate Prediction of T2DM According to Complex Clinical Variables

Variable	Complex Clinical Model 1		Complex Clinical Model 2		Complex Clinical Model 3	
	OR	*P* Value	OR	*P* Value	OR	*P* Value
Age, y						
<50	1 [Reference]		1 [Reference]		1 [Reference]	
50-64	1.02	.95	0.99	.96	1.03	.88
≥65	0.83	.53	0.81	.48	0.88	.67
Male	1.25	.26	1.12	.55	1.01	.98
Parental history of diabetes mellitus	1.63	.02	1.73	.01	1.71	.01
BMI						
<25.0	1 [Reference]		1 [Reference]		1 [Reference]	
25.0-29.9	1.08	.80	1.17	.61	1.19	.57
≥30.0	1.32	.45	1.80	.10	1.68	.15
Blood pressure >130/85 mm Hg or receiving therapy	1.53	.05	1.40	.13	1.58	.03
HDL-C level <40 mg/dL in men or <50 mg/dL in women	2.33	<.001	2.18	<.001	2.18	<.001
Triglyceride level ≥150 mg/dL	1.45	.07	1.50	.05	1.57	.03
Waist circumference >88 cm in women or >102 cm in men	1.32	.28	1.25	.38	1.27	.35
Fasting glucose level 100-126 mg/dL	5.37	<.001	5.32	<.001	5.09	<.001
2-Hour OGTT finding 140-200 mg/dL	2.87	<.001	NI		NI	
Fasting insulin level >75th percentile	1.23	0.33	NI		NI	
C-reactive protein level >75th percentile	1.43	0.07	NI		NI	
Log Gutt insulin sensitivity index <25th percentile	NI		2.28	<.001	NI	
Log HOMA insulin resistance index >75th percentile	NI		NI		2.05	.001
HOMA β-cell index <25th percentile	NI		NI		1.88	.002
Intercept	−5.506		−5.427		−5.620	
AROC	0.854		0.850		0.851	

Abbreviations: AROC, area under the receiver operating characteristic curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model; NI, not included; OGTT, oral glucose tolerance test; OR, odds ratio; T2DM, type 2 diabetes mellitus.
SI conversion factors: To convert HDL-C to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113.

Source: Wilson 2007

USPSTF Table 1. Summary of Evidence[a]

Variable		Design	Limitations	Consistency	Primary Care Applicability	Overall Quality	Summary of Findings
KQ1: overall effect of screening on final outcomes	3 studies.	Case–control and cross-sectional studies.	Data were limited; studies considered microvascular complications only.	Studies were consistent.	Case–control study was representative of a primary care population, but results did not represent population-level results from a screening program. Fair-quality cross-sectional study was a non-U.S. population in an area of high screening rates and national registries; however, an unknown percentage was clinically detected.	Poor	Both fair-quality studies demonstrated no benefit for screening: Case–control study: Patients with > 1 glucose screening event in 10 years had a 13% reduction in risk for severe microvascular T2DM complications. Cross-sectional study: No significant differences between T2DM population and general Swedish population (where there is a high level of screening for T2DM) in most measures of visual acuity. One poor-quality study showed NSD.
KQ2: diabetes treatment	8 studies.	RCTs with diabetes vs. nondiabetes (subgroup analyses); RCTs with duration of T2DM ≤ 1 y	Several studies were probably underpowered for the diabetes subgroup. Baseline characteristics differed between the diabetes and nondiabetes subgroups.	Studies generally showed no evidence of a significant differential effect between diabetes and nondiabetes subgroups.	Studies were representative of a primary care population, but results did not represent population-level results from a screening program.	Fair	Persons with T2DM without known CVD seem to benefit from aggressive lipid-lowering treatment as much as persons without T2DM with known CVD. There is little strong evidence that specific antihypertensive drugs benefit persons with T2DM more than those without. Persons with T2DM seem to benefit from a lower BP target than persons without. Fair evidence suggests a marginal benefit of aspirin for primary prevention of CVD, although no clear evidence suggests that those with diabetes benefit more than other subgroups at high risk for CVD.
KQ3: prediabetes	11 studies.	RCTs	Mean follow-up,	Lifestyle and drug	Trials consisted of highly selected	Fair	Intensive lifestyle and pharmacotherapeutic

USPSTF Table 1. Summary of Evidence[a]

Variable		Design	Limitations	Consistency	Primary Care Applicability	Overall Quality	Summary of Findings
treatment			approximately 3 years; longest follow-up, 7 years; only 3 studies examined long-term health outcomes.	interventions consistently produced a decrease in incidence of T2DM.	participants.		interventions reduce the progression of prediabetes to T2DM at follow-up up to 7 years. Few data exist on the effect of these interventions on cardiovascular events, death, or other long-term health outcomes.
KQ4: adverse effects of screening	8 studies	Cohort and cross-sectional studies	All observational studies; predominantly white; study samples composed of volunteers; short follow-up.	It is difficult to compare results across studies because of heterogeneous outcome measures and comparison groups; however, no serious adverse effects were noted.	Studies included persons at high risk for T2DM, so results may not be applicable to primary care populations.	Fair to poor.	Data were sparse on the psychological effects of screening for T2DM, and no available data suggested significant adverse effects at up to 1-year follow-up. No study reported serious, long-term, adverse effects of a new diagnosis of T2DM.
KQ5: adverse effects of treatment	24 studies.	Systematic reviews	Reviews were almost entirely based on trials of short to moderate duration; long-term data were lacking.	Not applicable; different drugs were examined in each review.	Included studies were largely trials of selected populations with limited applicability to real-world, primary care populations.	Fair	Acarbose: NSD in death from placebo; gastrointestinal side effects common. Metformin: NSD in death, hypoglycemia, lactic acidosis vs. placebo or diet. ACE-I: significant increase in cough vs. placebo. Beta-Blockers: increase in withdrawals secondary to adverse events vs. placebo; NSD in total deaths. Rosiglitazone: new data on potential for increased risk for cardiac events and heart failure.
a ACE-I = angiotensin-converting enzyme inhibitor; BP = blood pressure; CVD = cardiovascular disease; NSD = no significant difference; RCT = randomized, controlled trial; T2DM = type 2 diabetes mellitus.							

USPSTF Table 2. Number Needed to Screen for Type 2 Diabetes to Prevent 1

Adverse Event after 5 Years of Additional Treatment[a]

Prevalence of Undiagnosed Disease	Patient Population	Tight Glycemic Control to Prevent 1 Case of Blindness in 1 Eye (Screening 1000 People with Given Prevalence)			Tight Blood Pressure Control to Prevent 1 CVD Event (Screening 1000 Hypertensive People with Given Prevalence)		
		Increase in Persons with Tight Glycemic Control, %	Cases of Blindness Averted, *n*[b]	NNS	Increase in Persons with Tight Blood Pressure Control, %	CVD Events Averted, *n*[c]	NNS
2.8%	Standardized prevalence in U.S.[c]	50	0.06	16,420	50	0.53	1,905
		90	0.11	9,122	90	0.95	1,058
3.6%	Standardized prevalence in U.S. non-Hispanic black/African American persons[c]	50	0.08	12,771	50	0.68	1,481
		90	0.14	7,095	90	1.22	823
6.0%	Prevalence estimated for previous review	50	0.13	7,663	50	1.13	889
		90	0.23	4,257	90	2.03	494

[a] CVD = cardiovascular disease; NNS = number needed to screen.
[b] Relative risk reduction, 0.29 over 5 years; rate of blindness in no-treatment group, 1.5% over 5 years. Data on incidence of retinal photocoagulation in 1 eye from the United Kingdom Prospective Diabetes Study.
[c] Relative risk reduction of 0.50 over 5 years; 5-year incidence in usual treatment group, 7.5%. Data from the Hypertension Optimal Treatment trial.

USPSTF 2008 Table 3. Number Needed to Screen for Prediabetes to Prevent 1 Case of Diabetes after 3 Years[a]

Prevalence of IGT or IFG	Patient Population	Lifestyle Intervention to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)b			Metformin to Prevent 1 Case of Diabetes (Screening 1000 People with Given Prevalence)c		
		Increase in Persons Adhering to Intervention, %	Cases of Diabetes Delayed, n	NNS	Increase in Persons Adhering to Intervention, %	Cases of Diabetes Delayed, n	NNS
15.0%	IGT only, total U.S. population[d]	50	4.79	209	50	2.56	391
		90	8.61	116	90	4.60	217
26.0%	IFG only, total U.S. population[e]	50	8.29	121	50	4.43	226
		90	14.93	67	90	7.98	125
40.0%	Estimate IFG and/or IGT[f]	50	12.76	78	50	6.82	147
		90	22.97	44	90	12.28	81

[a] IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NNS = number needed to screen.
[b] Relative risk reduction, 58%; 38% achieved weight loss goal of 7% at end of 3-year follow-up (intention-to-treat analysis); control rate, 11%. Data from the Diabetes Prevention Program.
[c] Relative risk reduction, 31% with adherence rates (≥ 80% of medications taken); 77% in control group; 72% in intervention group. Data from the Diabetes Prevention Program.
[d] Based on National Health and Nutrition Examination Survey, 1994 data.
[e] Prevalence data from National Health and Nutrition Examination Survey, 2002 (1): IFG, 5.5–6.93 mmol/L (100–126 mg/dL).
[f] From National Institute of Diabetes and Digestive and Kidney Diseases, 1994 data (http://diabetes.niddk.nih.gov/dm/pubs/statistics).

2007 Guideline:

For the 2007 update, no new evidence was found; the recommendation remains unchanged from the 2005 guideline.

- The 2003 US Preventive Services Task Force[20] recommends screening for type 2 diabetes in adults with hypertension, because of evidence that, in adults with hypertension and clinically detected diabetes, lowering blood pressure below conventional target blood pressure values reduces the incidence of cardiovascular (CV) events and CV mortality.*
- The 2003 US Preventive Services Task Force[20] also recommends screening for type 2 diabetes in patients with hyperlipidemia, because of evidence that detecting diabetes improves estimates of individual risk for coronary heart disease, which is an integral part of decisions about lipid lowering therapy.
- Although there is evidence that development of diabetes can be delayed in patients with impaired glucose control, there is no evidence that treating diabetes prior to the onset of typical diabetes symptoms will reduce or prevent diabetes outcomes. Thus, screening asymptomatic patients with other risk factors is optional.

Other Considerations

The ADA has defined high-risk diabetes status as a family history of type 2 diabetes in first- and second-degree relatives; belonging to a certain racial/ethnic group (Native Americans, African Americans, Hispanic Americans, or Asians/South Pacific Islanders); or having signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome).[21]

5. Test to Screen for Diabetes and Pre-Diabetes

5A If a test for diabetes and pre-diabetes is desired, a Fasting Plasma Glucose (FPG) test is currently recommended. A HbA1c is also an acceptable alternative. *Consensus-based*

5B HbA1c is now accepted as a standard routine screening test. *Consensus-based*

Rationale:

2009 Update:

The role of HbA1c as a screening test will likely be re-evaluated as a mid cycle update later this year. Thus, these recommendations were revised.

2007 Update:

No new evidence was found, the recommendation remain unchanged.

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* Adapted from: U.S. Preventive Services Task Force. Screening for Type 2 Diabetes Mellitus in Adults: Recommendations and Rationale. February 2003. Agency for Healthcare Research and Quality, Rockville, MD. Used with permission. http://www.ahrq.gov/clinic/3rduspstf/diabscr/diabetrr.htm

2005 Update:

- There is no evidence that shows the effect of IFG or oral glucose tolerance on health outcomes.
- There is some overlap of patients that have impaired fasting glucose and IGT; however, there are situations where neither test will pick up all patients with abnormal glucose metabolism.
- Given the simplicity of fasting glucose, the GDT decided it is the test of choice. However, physicians may use individual discretion to test with an oral glucose tolerance test if fasting glucose is normal.

Other Considerations

The ADA states that HbA1c does not have a role in screening.[21]

Pharmacological Management of Diabetes

6. Blood Pressure Threshold to Initiate Drug Therapy in Patients with Diabetes and Hypertension

6A The GDT recommends initiating antihypertensive drug therapy in patients with diabetes with a systolic blood pressure of ≥ 140 mmHg and/or diastolic ≥ 85 to 90 mmHg. *Consensus-based*

6B After three months of lifestyle therapy, if systolic BP is 130 to 139 or diastolic BP is 80 to 89, initiate drug therapy. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

Although no studies were found that compared treatment of people with diabetes and higher blood pressure with treatment of those with lower blood pressure, clinicians need to know when to initiate therapy in order to effectively treat hypertension.

Other Considerations

The GDT decided to recommend a threshold for initiation of antihypertensive therapy above that of the treatment goal.

Given the risk of poor cardiovascular outcomes related to high blood pressure, it is reasonable to use the American Diabetes Association criteria of 140/90 mmHg as a starting point for treating hypertensive patients with diabetes.[22]

7. Blood Pressure Threshold to Initiate Combination Drug Therapy in Patients with Diabetes and Hypertension

7 When BP is ≥ 150 to 160/90 mmHg, the GDT recommends initiating therapy with two drugs, either as a separate prescription or in fixed dose combinations. *Consensus-based*

Note: For patients with diabetes and hypertension, the target blood pressure is < 130/80 mmHg.

Rationale:

2007 Update

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- No studies were found that compared combination treatment of people with diabetes and blood pressure (BP) more than 20/10 mmHg above goal to those with single therapy treatment and BP more than 20/10 mmHg above goal.
- Given the risk of poor cardiovascular outcomes related to high blood pressure, the GDT decided to use the American Diabetes Association criteria of 140/90 mmHg as a starting point for treating hypertensive patients with diabetes.
- Given the high proportion of patients with diabetes who will need polytherapy to control BP, the GDT also recommends a threshold to initiate combination therapy.
- According to JNC 7: "When BP is more that 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs, either as a separate prescription or in fixed dose combinations."[23]

8. Initial Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease or Microalbuminuria

8A The GDT strongly recommends a thiazide-type diuretic for the treatment of diabetes and hypertension (HTN) in the absence of heart failure, known coronary heart disease, or microalbuminuria. *Evidence-based: A*

8B The GDT has determined that because most individuals with HTN and diabetes will need more than one drug to control their HTN effectively, combination therapy with HCTZ/ACE inhibitors as first-line therapy is an option. *Consensus-based*

Rationale:

Evidence for Recommendation 8A: Good

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- One follow-up analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was found.[24] There was no significant difference in the incidence of fatal CHD and nonfatal MI for patients assigned to chlorthalidone (diuretic) to lisinopril (ACE inhibitor) or to amlodopine (calcium channel blocker). There was no significant difference in the incidence of total mortality, end-stage renal disease, or cancer between the three groups. Heart failure was more common in diabetes patients assigned to amlodopine [1.39 (95% CI: 1.22 to 1.59)] vs. chlorthalidone.
- Trials which compared calcium channel blockers vs. beta-blockers[25, 26] and calcium channel blockers vs. diuretics,[27] were also identified, but no significant results were found. In a retrospective analysis of the SHEP trial,[28] diuretic treatment compared with placebo in patients with diabetes led to a significantly lower long-term CV mortality rate and total mortality rate.

Supporting Evidence for ACE Inhibitors vs. Diuretics

- The ALLHAT trial[29] was a large scale RCT (n = 12,063: diabetes subgroup) which found no significant difference between diuretics and ACE inhibitors (angiotensin converting enzyme inhibiters) in the prevention of major coronary events, mortality, or stroke in patients with diabetes and hypertension. When compared with ACE inhibitors, diuretics significantly reduced heart failure outcomes in the diabetes subgroup.
- The ALLHAT trial compared chlorthalidone (diuretics) to lisinopril (ACE inhibitors) and to amlodopine (calcium channel blockers) in people age ≥ 55 who had stage 1 or stage 2 hypertension with at least one additional risk factor for CHD events. The additional risk factor included a history of type 2 diabetes, previous MI or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, current cigarette smoking, high density lipoprotein cholesterol < 35 mg/dL, or documentation of other atherosclerotic CVD. Of the total study population 36% (n = 12,063) were patients with diabetes.

Results:

In the diabetes subgroup, ACE inhibitors when compared with diuretics were associated with the following results:

- No significant difference in the primary outcome (fatal or nonfatal MI, or all-cause mortality) [RR = 1.00; (95% CI: 0.87 to 1.14)].
- No significant difference in all-cause mortality [RR = 1.02; (95% CI: 0.91 to 1.13)].
- No significant difference in combined CHD (nonfatal MI, CHD death, coronary revascularization, hospitalized angina) [RR = 1.03; (95% CI: 0.93 to 1.15)].
- No significant difference in stroke [RR = 1.07; (95% CI: 0.90 to 1.28)].
- No significant difference in combined CVD events (nonfatal MI, CHD death, stroke, coronary revascularization, hospitalized or treated angina, treated or hospitalized heart failure and peripheral arterial disease) [RR = 1.08; (95% CI: 1.00 to 1.17)].
- Significant reduction in the risk of HF outcomes (when using diuretics, as compared with ACEI) [RR = 1.42; (95% CI: 1.23 to 1.64)].
  - The diabetes subgroup analysis for the ALLHAT trial was not published at the time of this guideline revision.
  - Because the ALLHAT study population was not a pure diabetes population, the diabetes subgroup was not randomized, and the diabetes subgroup analysis with renal outcomes has not yet been published, there is not enough evidence to favor diuretics over ACE inhibitors at this time.

Supporting Evidence for ARB vs. Beta-Blockers

- No evidence was found that compared ACE inhibitors to ARB in people with diabetes and hypertension.
- One large RCT (LIFE)[30] found that losartan (representing ARBs) was more effective than atenolol (representing beta-blockers) in reducing the risk of CV mortality and morbidity in patients with diabetes and hypertension. However, since there is no strong evidence to suggest that beta-blockers should be recommended as first-line therapy in patients with diabetes and hypertension, ARBs also cannot be recommended as initial therapy at this time.

  LIFE Study Characteristics
  - Parallel-group trial of (n = 1,195) patients (aged 55 to 80 years) with diabetes, hypertension, and signs of left ventricular hypertrophy on electrocardiograms.
  - Patients were randomized to receive losartan 50 mg or atenolol 50 mg. After two months, hydrochlorothiazide (HCTZ) 12.5 mg was added if blood pressure was not at, or below, goal blood pressure. After four months, the dose of losartan or atenolol was doubled to 100 mg plus HCTZ 12.5 mg if blood pressure was still inadequately controlled. At month six, additional open-label antihypertensive medication, including upward titration of HCTZ, was added in order to reach goal blood pressure.

  LIFE Study Results

  When compared with beta-blockers, ARBs were associated with the following:
  - Statistically significant reduction in the primary composite endpoint (CV mortality, stroke, and MI) [HR = 0.76; (95% CI: 0.58 to 0.98)].
  - Statistically significant reduction in CV mortality [HR = 0.63; (95% CI: 0.42 to 0.95)].
  - Statistically significant reduction in total mortality [HR = 0.61; (95% CI: 0.45 to 0.84)].
  - Statistically significant reduction in hospitalization for heart failure [HR = 0.59; (95% CI: 0.38 to 0.92)].

Supporting Evidence for Antihypertensive Therapy vs. Placebo

- Several large RCTs were found that show antihypertensive drugs decrease morbidity and mortality in people with diabetes and hypertension when compared with placebo.[31, 32]

Supporting Evidence for ACE Inhibitors vs. Calcium Channel Blockers

- One systematic review[33] from BMJ's Clinical Evidence was found that included an earlier systematic review by Pahor[34] and one subsequent RCT[35] that compared ACE inhibitors to calcium channel blockers (CCBs). The Pahor systematic review included two studies that compared ACE inhibitors to calcium channel blockers and two studies that compared ACE inhibitors to beta-blockers.
  - Pahor, et al.[34] included two RCTs that compared an ACE inhibitor to a CCB: Estacio, et al.[36] (ACE inhibitor enalapril vs. CCB nisoldipine), and Tatti, et al.[37] (ACE inhibitor fosfinopril vs. CCB amlodipine). The subsequent RCT by Lindholm, et al.[35] compared ACE inhibitor vs. CCB (felodipine or isradipine) vs. conventional treatment (beta-blocker or hydrochlorothiazide plus diuretic). Study durations ranged from 3.5 to 5.6 years.
  - Inclusion criteria varied per study. Estacio included both hypertensive (n = 470) and non-hypertensive (n = 480) people with type 2 diabetes (age range 40 to 74), while Tatti limited the study population to people with type 2 diabetes and hypertension (n = 380; mean age approximately 63). Lindholm included a diabetes subgroup within his study population of older adults people with hypertension (n = 719; age 70 to 84, mean age 75.8).

- Both Estacio and Tatti found ACE inhibitor to be superior to CCB in reducing CV events (calculations supplied by Clinical Evidence: RR = 0.49; (95% CI: 0.33 to 0.72); NNT = 13; (95% CI: 7 to 25) between 3.5 to 5.6 years). There was also a greater decrease in death, acute myocardial infarction (AMI), and stroke with ACE inhibitors, but the reduction was not statistically significant.
- Lindholm found the effect of ACE inhibitor and CCB to be similar for cardiovascular mortality and stroke. However, there were significantly fewer MIs during ACE inhibitor treatment than CCB treatment (RR = 0.51; (95% CI: 0.28 to 0.92); p = 0.025).
  - ACE inhibitors have been shown to reduce CV events, including AMI, when compared with CCB in populations that were either exclusively people with diabetes[37] or that included people with diabetes.[35, 36] Therefore, ACE inhibitors are recommended over CCB in the treatment of hypertension.
  - The GDT concluded that the results presented in the above studies should equally apply to the general diabetes population even though they do not compare ACE inhibitor to CCB in people with type 1 diabetes, or adults under the age of 40.

Supporting Evidence for ACE Inhibitors vs. Beta-Blockers

- One systematic review[33] from BMJ's Clinical Evidence was found that included an earlier review by Pahor, et al.[34] Pahor included CAPPP[38] and UKPDS 39[39] which compared ACE inhibitors to beta-blockers.
  - CAPPP compared ACE inhibitor (captopril) to conventional therapy (beta-blocker [atenolol or metoprolol] plus diuretic [hydrochlorothiazide or bendrofluazide] if necessary) and UKPDS 39 compared ACE inhibitor (captopril) to a beta-blocker (atenolol).
  - CAPPP included a subgroup of 572 people with diabetes (either type 1 or 2), ages 25 to 66, with treated or untreated hypertension (diastolic blood pressure was 100 mmHg on two separate occasions). The mean follow-up period was 6.1 years.
  - UKPDS 39 included 758 people with hypertension and type 2 diabetes (mean age 58), with and without microalbuminuria, who were followed for a mean 8.4 years.
  - In the CAPPP study, ACE inhibitor was associated with a risk reduction for MI of 0.34; (95% CI: 0.17 to 0.67; p = 0.002) and a risk reduction for all fatal events of 0.67; (95% CI: 0.46 to 0.96; p = 0.030). There was no statistically significant difference between treatment groups for stroke.
  - UKPDS 39 did not show the same results. ACE inhibitors did not significantly reduce CV events (RR = 1.22; 95% CI: 0.94 to 1.58) nor proteinuria (p = 0.31 for urinary albumin concentration = 50 mg/l and p = 0.090 for clinical proteinuria = 300 mg/l) when compared with beta-blockers. There was more weight gain associated with beta-blockers but no difference found between beta-blockers and ACE inhibitors in rates of hypoglycemia, lipid concentrations, tolerability, blood pressure lowering, or prevention of disease events.
    - There are conflicting data on ACE inhibitors vs. beta-blockers. The CAPPP study indicated that ACE inhibitors are superior to beta-blockers (plus diuretics if necessary), while UKPDS 39 suggested that ACE inhibitors and beta-blockers are similarly efficacious. Because of the results of CAPPP and the weight gain associated with beta-blockers,[38] the GDT recommends ACE inhibitors as the first-line choice for treating hypertension in people with diabetes.

Overall Conclusion

Thiazide diuretics are the preferred choice for first-line treatment of diabetes and hypertension, but 40 to 60% of the population will need a second drug to achieve blood pressure control, regardless of the first-choice drug. To this end, many drug trials, such as the ALLHAT trial[29] and the SHEP trial[28] have used thiazide-type diuretics in combination with ACEIs or BBs as two-drug combination therapy, and have demonstrated effectiveness. Based upon the information provided in these two large-scale RCTs (ALLHAT,[29] SHEP[28]) the GDT recommends HCTZ/ACE inhibitors as first-line combination therapy for individuals with diabetes and hypertension who need more than one drug to control their hypertension effectively.

Other Considerations

- Recent trials suggest that overall blood pressure control is important regardless of which agent is used as first-line therapy. In trials where a low target blood pressure was the goal, combination therapy of antihypertensive agents was required to achieve the target.[40, 41] The order of combination therapy varied per study.
- ACE inhibitors are generally considered to have a "class" effect due to the cardiovascular protective and antihypertensive properties that each brand studied has shown. No studies were found that compare different brands of ACE inhibitors and it is unlikely that any such studies will be conducted in the near future.
- There are two types of CCBs, dihydropyridine and non-dihydropyridine. Neither type of CCB has been shown to be as effective as ACE inhibitor in treating hypertension.
- There are two types of beta-blockers, cardioselective and non-cardioselective. Both studies included in this systematic review used cardioselective beta-blockers. All cardioselective beta-blockers are generally considered to have a similar effect to each other in people with diabetes and hypertension.

9. Step Therapy in the Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease

9 The GDT recommends:

<u>For two drugs:</u> If blood pressure is not controlled on a thiazide-type diuretic alone, then a thiazide-type diuretic + ACEI is recommended.

<u>For three drugs:</u> If blood pressure is not controlled on a thiazide-type diuretic + ACEI, then adding a dihydropyridine calcium channel-blocker is recommended.

<u>For four drugs:</u> If blood pressure is not controlled on a thiazide-type diuretic + ACE inhibitor + dihydropyridine calcium channel-blocker, then adding a beta blocker or spironolactone is recommended.

Consensus-based

Rationale:

2009 Update:

These recommendations are excerpted from the 2009 KP National Hypertension Clinical Practice Guidelines. KP National is working towards complete alignment and integration of recommendations among the Diabetes, CAD, Hypertension and Dyslipidemia Guidelines, under the oversight of the Integrated Cardiovascular Health Leads (John Merenich, MD, Marc Jaffe, MD, Jim Dudl MD, John Golden MD, Joel Handler MD, and Wiley Chan MD).
The first step in this process is to align the mostly minor discrepancies between the existing recommendations that address the same topic. The Diabetes Guideline had several recommendations that had been updated by the other GDTs, and the ICVH Leads felt that it would be best to formally adopt those updated recommendations in the Diabetes Guideline.

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- No studies were found that randomized patients with diabetes and hypertension who were already controlled on a first-line agent to a second drug. Most drug trials are not confined to monotherapy, but few, if any, randomize and report outcomes in terms of specific combinations of drugs.
- Recent trials suggest that overall blood pressure control is more important than which agent is used first.[41] In most trials, combination therapy was required to achieve target blood pressure. Given the efficacy of diuretics and ACE inhibitors in reducing blood pressure, clinical events as well as their tolerability, either diuretics or ACE inhibitors should be included in all multidrug regimens.
- There is limited evidence demonstrating the effectiveness of ARBs compared with first-line medications. The LIFE trial[30] compared an ARB to a beta-blocker, but did not compare them to diuretics, ACE inhibitors, or to CCBs. The LIFE trial enrolled only a subset of all hypertensive patients, those with left ventricular hypertrophy (LVH), and demonstrated slightly improved outcomes of ARBs compared with beta-blockers.
- There is strong evidence of the effectiveness of ACE inhibitors, diuretics, beta-blockers, and ARBs in reducing BP and lowering the complications of hypertension.[29, 32, 39, 42-45] However, when clinical outcomes are similar among medications, factors, such as side effects, tolerability, and drug costs can be used to select an appropriate stepwise approach. Based on the high cost of ARBs, the GDT recommends beta-blockers over ARBs when a third drug is needed.

10. Drug Therapy for Patients with Diabetes, Hypertension, and Microalbuminuria or Diabetic Nephropathy

10 The GDT recommends that if a person with diabetes, hypertension, and microalbuminuria (or albuminuria) is intolerant to an ACE inhibitor, then, in the absence of contraindications, an ARB be substituted to prevent progression of renal disease. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

One study[46] was found that further analyzed CV outcomes in the Irbesartan Diabetic Nephropathy Trial (IDNT) for patients with type 2 diabetes and overt nephropathy. The three groups (irbesartan, amlodopine, or placebo) were not statistically different in the composite of CV events. However, there was a significantly decreased incidence of congestive heart failure for irbesartan when compared with placebo recipients [HR = 0.72; (95% CI: 0.52 to 1.00, p = 0.048)] or amlodipine recipients [HR = 0.65; (95% CI: 0.48 to 0.87)].

Definitions of microalbuminuria and clinical albuminuria as defined by the ADA and National Kidney Foundation:[21, 47]

Category	24-h collection (mg/24-h)	Timed Collection (mcg/min)	Spot Collection (mcg/mg creatinine)
Microalbuminuria	30 to 300	20 to 200	30 to 300
Albuminuria	>300	>200	>300

Supporting Evidence for use of Angiotensin II Blockers (ARBs) in People Intolerant to ACE Inhibitors

- No studies were found that compared ARBs in people who were intolerant to ACE inhibitors. To determine if ARBs and ACE inhibitors are interchangeable in people with hypertension, diabetes, and microalbuminuria (or albuminuria); the GDT looked for guidance from studies that examined the effect of these two drugs on kidney function in this specific subpopulation.
- Both ACE inhibitors and ARBs have been shown to have a positive effect on people with diabetes, hypertension, and microalbuminuria when compared with placebo. ARBs have been shown to reduce the risk of ESRD (end-stage renal disease) when compared with placebo[48, 49] and ACE inhibitors reduce the risk of overt nephropathy.[32] Several studies have recently been published[50, 51] that raised the question of whether the ARBs and ACE inhibitors are interchangeable in this subpopulation because both ACE inhibitors and ARBs have a similar effect on microalbuminuria.
- The GDT also looked at any other studies that compared the use of antihypertensive agents to ARB in people with hypertension, diabetes, and microalbuminuria (or albuminuria).
- No studies with direct evidence were found, so the GDT looked at studies comparing the efficacy of ACE inhibitors compared with ARBs.

Supporting Evidence for ACE Inhibitors vs. Angiotensin II blockers (ARBs)

- Two small studies were found that compared ACE inhibitors to ARBs in people with diabetes, hypertension, and microalbuminuria or albuminuria.[50, 51]
- Andersen[50] included 16 patients with type 1 diabetes, hypertension, and albuminuria in a cross-over study.
- The study compared placebo, two different doses of ARB (losartan), and two different doses of ACE inhibitor (enalapril). The study was small and the follow-up period was short (ten months).
- Serum creatinine and 24-hr urinary albumin were significantly better during the periods the participants were on drug therapy compared with placebo. Unfortunately, no results that compared ACE inhibitor to ARB were reported.
- The CALM study[51] randomized 199 people with type 2 diabetes, hypertension, and microalbuminuria to ACE inhibitor (lisinopril), ARB (candesartan), or combination ACE inhibitor/ARB (lisinopril plus candesartan).
- The study was short-term (24 weeks) and the only relevant end point reported was adjusted mean urinary albumin: creatinine ratio.
- The adjusted mean urinary albumin: creatinine ratio was statistically significantly better with combination ACE inhibitor/ARB than ARB alone ($p = 0.04$) but not when combination therapy was compared with ACE inhibitors alone ($p = 0.20$). No difference was found between groups for creatinine clearance.
- There is not enough evidence to recommend that ACE inhibitors and ARBs are inter-changeable in this subpopulation of people with diabetes and hypertension, therefore the GDT recommends substitution of ARBs for ACE inhibitors only when ACE inhibitors are not well tolerated.

Supporting Evidence for Calcium Channel Blockers (CCBs) vs. Angiotensin II Blockers (ARBs)

One randomized, controlled trial was found that compared placebo, CCBs, and ARBs.[52]

- The IDNT study[53] compared ARB (irbesartan) to CCB (amlodipine) in 1,715 patients with type 2 diabetes, nephropathy (≥ 900 mg 24-hr urine protein excretion or serum creatinine), and hypertension. The follow-up period was 2.6 years and the outcomes of interest were ESRD, doubling of serum creatinine, and death.
- For ESRD, a relative risk reduction of 0.83 (95% CI: 0.62 to 1.11; $p = 0.19$) was associated with ARB compared with placebo and 0.76 (95% CI: 0.57 to 1.02; $p = 0.06$) for ARB compared with CCB. CCB did not cause a statistically significant relative risk reduction when compared with placebo (RR = 1.07; 95% CI: 0.89 to 1.29; $p = 0.47$).
- A relative risk reduction of 0.71 (95% CI: 0.54 to 0.92; $p = 0.009$) for doubling of serum creatinine was associated with ARB compared with placebo and 0.61 (95% CI: 0.48 to 0.79; $p < 0.001$) for ARB compared with CCB. CCB did not cause a statistically significant reduction in relative risk when compared with placebo (RR = 1.15; 95% CI: 0.91 to 1.46; $p = 0.24$).
- There was no statistically significant difference in reduction of death with any group.
- CCBs can not be recommended as a substitute for ACE inhibitors or ARBs in this subpopulation of people with diabetes and hypertension because CCB did not have a positive effect on kidney function when compared with placebo or ARB.

Other Considerations

- Doubling serum creatinine was found to be associated with increased mortality, dialysis, and kidney transplantation.[54] A statistically significant correlation was found between decreased survival and elevated urinary albumin concentration (microalbuminuria and proteinuria) in people with diabetes. Microalbuminuria is predictive of clinical proteinuria and increased mortality.[55]
- ACE inhibitors are generally considered to have a "class" effect due to the cardiovascular protective, antihypertensive, and renoprotective properties demonstrated by each brand of ACE inhibitor that has been studied. No studies were found that compare different brands of ACE inhibitors and it is unlikely that any such studies will be conducted in the near future.
- The effect of ARBs is generally considered a "class" effect because of their renoprotective properties.

11. Target Blood Pressure for People with Diabetes and Hypertension

11 The GDT recommends that the target blood pressure be < 130/80 mmHg for patients with diabetes and hypertension.
Evidence-based: A – (Diastolic Blood Pressure)
Consensus-based – (Systolic Blood Pressure)

Rationale:

Evidence for Recommendation 11: Good

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- One systematic review[33] in Clinical Evidence included two RCTs[40, 41] that compared varying target blood pressures.
- UKPDS 38[41] included patients with type 2 diabetes and hypertension, with and without microalbuminuria.
- 758 patients were randomized to tight control (≤ 150 / ≤ 85 mmHg) and 390 patients to less tight control (≤ 180 / ≤ 105 mmHg). Follow-up was 8.4 years.
- Tight control was associated with fewer MIs (NNT = 14; 95% CI: 9 to 35) and strokes (NNT = 27; 95% CI: 18 to 116).
- The HOT trial[40] focused on lowering diastolic blood pressure in patients with hypertension.
- 1,503 patients with type 1 or type 2 diabetes were included and followed for 3.8 years.
- The target for tight control was ≤ 80 mmHg and the less tight control was ≤ 90 mmHg.
- Tight control was associated with fewer MIs, stroke, and other CV death (NNT = 22; 95% CI: 16 to 57).

Other Considerations

- Although there is evidence that diastolic blood pressure should be lowered to at least 80 mmHg in hypertensive patients with diabetes, the consensus is that the target blood pressure should be < 130/80 mmHg.
- The target diastolic of 80 mmHg is evidence-based and the target systolic of 130 mmHg is a consensus opinion based on ADA and National Kidney Foundation recommendations.[21, 47]
- There is no evidence that a lower target systolic or diastolic blood pressure is harmful to people with diabetes and hypertension.

- A lower target blood pressure will likely require more drugs (more than one drug was used to achieve blood pressure goals in the above studies). When more than one drug is used, clinicians should consider compliance issues, adverse events associated with multiple antihypertensives, and cost.

12. Drug Therapy for Microalbuminuria in Normotensive Patients

12A In normotensive adults under age 55 who have diabetes and microalbuminuria, an ACE inhibitor is recommended to prevent progression to end-stage renal disease. *Consensus-based*

12B In normotensive adults with diabetes, microalbuminuria (or albuminuria) and ACE inhibitor allergy or intolerance, there is insufficient evidence to recommend for or against the use of angiotensin receptor blockers to prevent progression to end-stage renal disease. *Evidence-based: I*

Evidence Grade[*]

Evidence for Recommendation 12B: Insufficient

2009 Update

New evidence has been identified. Recommendations have been changed based on both new evidence and expert/consensus opinion.

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. See Appendix B for more information on the search strategy.

Executive Summary

There is good evidence that ACE inhibitors prevent the progression of microalbuminuria in normotensive patients with diabetes. However, there is insufficient evidence that ACE inhibitors prevent the hard outcomes of increasing of serum creatinine or progression to ESRD. Therefore, the GDT debated the clinical value of preventing progression of microalbuminuria in a population ≥ 55 years of age, with diabetes and risk factors including, but not limited to, microalbuminuria - a population not specifically encompassing all those patients addressed in the problem formulation here, and in the absence of sufficient direct evidence, makes a consensus-based recommendation to use ACE inhibitors to prevent progression to ESRD. There is insufficient evidence for the GDT to recommend for or against use of ARBs in this group, whether or not they are intolerant of ACE inhibitors.

[*] The criteria for grading the strength of the evidence as either "good," "fair," or "insufficient" adheres to the KP National Guideline Program's "Policies and Procedures" documents entitled "Label and Language of Recommendations" and "KP System for Grading the Strength of a Body of Evidence," which are located in Appendix A.

Rationale

No studies were identified that directly addressed the primary health outcomes of interest in this problem formulation. However, a comprehensive systematic review of the literature identified two low-quality trials [56, 57] that addressed the intermediary outcomes of interest, i.e., the effect of ARBs on microalbuminuria in normotensive patients with diabetes and microalbuminuria. The findings of these studies, however, are compromised by their methodological shortcomings. A 2009 position statement from the American Diabetes Association was also identified and is included in the review below. Furthermore, a manual search yielded a 2005 meta-analysis by Casas et al., not previously addressed in this guideline, which asserts that the positive effect of ACE inhibitors and ARBs is a result of their antihypertensive qualities and their cardio-protective effect and not necessarily on their reno-protective effect. Even though studies included in this meta-analysis did not exclude hypertensive patients, as did the problem formulation here, they are included to provide a general overview of the role of ACE inhibitors and ARBs in microalbuminuria (or albuminuria) in patients with diabetes. None of the studies reviewed here addressed the adverse effects of intervention, i.e., rash, persistent dry cough, azotemia, hyperkalemia, or dialysis as an outcome of the intervention.

In a 6-month, prospective RCT with 2-month follow-up, **Agha et al.**[56] compared the anti-microalbuminuric effect of 50 mg/d losartan (an ARB) to placebo (500 mcg/d vitamin B-12) in non-insulin-dependent, normotensive patients with type 2 diabetes and microalbuminuria (N = 383). Microalbuminuria was defined as urinary excretion rate of 20 to 200 mcg/min or 24-hr urinary albumin of 30 to 300 mg/dL. Details regarding administration of medication to patients were not provided. Urinary microalbumin levels were recorded at baseline, at the end of the 6-month study, and two months after stopping losartan. Intent-to-treat analysis was not performed to account for the 22 patients lost to follow-up (19 in the test group, 2 in the control group).

In the test group, 87% (149/171) of patients experienced > 30% reduction of albuminuria; 8.2% (14/171) experienced 10 to 30% reduction; and 4.7% (8/171) experienced minimal or no change. In the placebo group, 1.6% (3/190) experienced > 30% reduction of albuminuria; 17.9% (34/190) experienced 10 to 30% reduction; and 76.5% (153/190) experienced minimal or no change. The statistical significance of the difference in urinary microalbumin before and after treatment with losartan was not assessed. The P-value for the difference between the results of the intervention and control groups was calculated and found to be statistically significant (P < 0.0001). In the initial week of treatment, lightheadedness was reported by 15 patients in the treatment group. This study suffered from detection bias, as it did not conduct power calculations. In addition, it did not conduct thorough statistical analyses on individual outcomes, to provide confidence intervals and p-values to determine significance of effect. There was also study procedure bias because neither patients nor intervention administrators were blinded. There may have also been a threat to its external validity resulting from multiple treatment interference with the oral diabetes medication of the study participants.

Table 1: Characteristics of Test Group at Baseline, After 6 Months of Losartan Use, and 2 months After End of Losartan Use

Lab/Physical Exam Characteristics	Baseline Mean ±SD (n = 171)	After 6 mos. Losartan Mean ±SD (n = 171)	2 months after stopping losartan Mean ±SD (n = 142)
SBP (mmHg)	134.3 ±8.6	131.1 ±12.6	132.6 ±10.9
DBP (mmHg)	82.3 ±11.4	78.6 ±13.4	79.7 ±10.3
Serum creatinine (mg/dL)	1.2 ±0.3	1.3 ±0.4	1.3 ±0.3
Random blood sugar (mg/dL)	182.9 ±81.4	161.3 ±51.2	173.1 ±63.8
Fasting blood sugar (mg/dL)	122.5 ±41.7	112.5 ±26.5	115.8 ±31.1
Serum Potassium (mEq/L)	4.3 ±0.8	4.4 ±1.1	4.2 ±0.9
24-hour urinary microalbumin (md/dL)	101.9 ±21.7	47.5 ±12.9	91.8 ±17.3

Table 2: Characteristics of Control Group at Baseline, After 6 Months of Losartan Use

Lab/Physical Exam Characteristics	Baseline Mean ±SD (n = 190)	After 6 mos. Mean ±SD (n = 190)
SBP (mmHg)	136.2 ±7.9	134.1 ±10.1
DBP (mmHg)	82.6 ±10.1	81.3 ±9.4
Serum creatinine (mg/dL)	1.2 ±0.5	1.3 ±0.3
Random blood sugar (mg/dL)	192.9 ±67.4	178.7 ±58.2
Fasting blood sugar (mg/dL)	121.9 ±33.8	119.7 ±24.8
Serum Potassium (mEq/L)	4.9 ±0.9	4.6 ±1.1
24-hour urinary microalbumin (mg/dL)	104.7 ±26.3	103.9 ±22.9

Difference between 24-hr urinary microalbumin in treatment group vs. control group was statistically significant ($P < 0.0001$).

Makino et al. [57] conducted a post-ad hoc analysis of the INNOVATION study (2005), to determine the anti-microalbuminuric effect of telmisartan (an ARB) on normotensive and hypertensive Japanese patients with type 2 diabetes and microalbuminuria. The INNOVATION study was a double-blinded, multi-center RCT which identified that telmisartan effectively reduced the transition rate from incipient to overt nephropathy in patients with diabetes. Microalbuminuria was defined as urinary albumin-to-creatinine ratio (UACR) of 100 to 300 mg/g creatinine). This review will only address the normotensive patients studied. A total of 163 normotensive, microalbuminuric patients were randomized to 40 mg/d or 80 mg/d or placebo for a 52-week period, with a mean follow-up of 1.3 years. The authors report but do not provide data to show that serum creatinine and creatinine clearance did not significantly change throughout the study. **The UACR in both the 40 mg (n = 58) and the 80 mg (n = 51) telmisartan groups decreased significantly ($p < 0.05$)** (see Fig.1 and Fig. 2 below, hard data not provided). **The 52-week measurement of UACR was significantly less in the telmisartan groups than in the placebo group (40 mg: 136 ±124.3; 80 mg: 112 ±113.7; placebo: 204 ±140.3, $p < 0.05$). No dose-dependent difference in UACR was observed.** Furthermore, in comparison to placebo, treatment with telmisartan showed lower transition rates to overt nephropathy and increased the revision rate to normoalbuminuria (statistically insignificant p not reported on latter).

Treatment with the 80 mg dose demonstrated statistically insignificant transition and remission rates compared to the 40 mg dose. Adverse events including but not limited to eye disorders, gastrointestinal disorders, infections, poisoning, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders were observed in 92.2% of the entire study population (485/526). In the normotensive population, 17.6% (9/51) of the telmisartan 80 mg group, 8.6% (5/58) of the telmisartan 40 mg group, and 13% (7/54) of the placebo group discontinued treatment due to adverse events. This study suffered from detection bias, as it did not conduct power calculations. In addition, it did not calculate confidence intervals to determine significance of effect. There may have also been a threat to its external validity resulting from multiple treatment interference with the oral diabetes medication of the study participants. The small number of patients in the three arms of the study is also notable. Furthermore, the patient recruitment and randomization process is not well-defined.

Table 3: Effect of Telmisartan on Transition and Remission from Microalbuminuria at Last Observation

	Placebo N = 54	Telmisartan 40 mg N = 58	Telmisartan 80 mg N = 51
Transitions n, (%)	18 (33.3)	7 (12.1)*	5 (9.8)*
Normalizations n, (%)	1 (1.9)	9 (15.5)*	10 (19.6)*

* Statistical difference from placebo group at $p < 0.01$

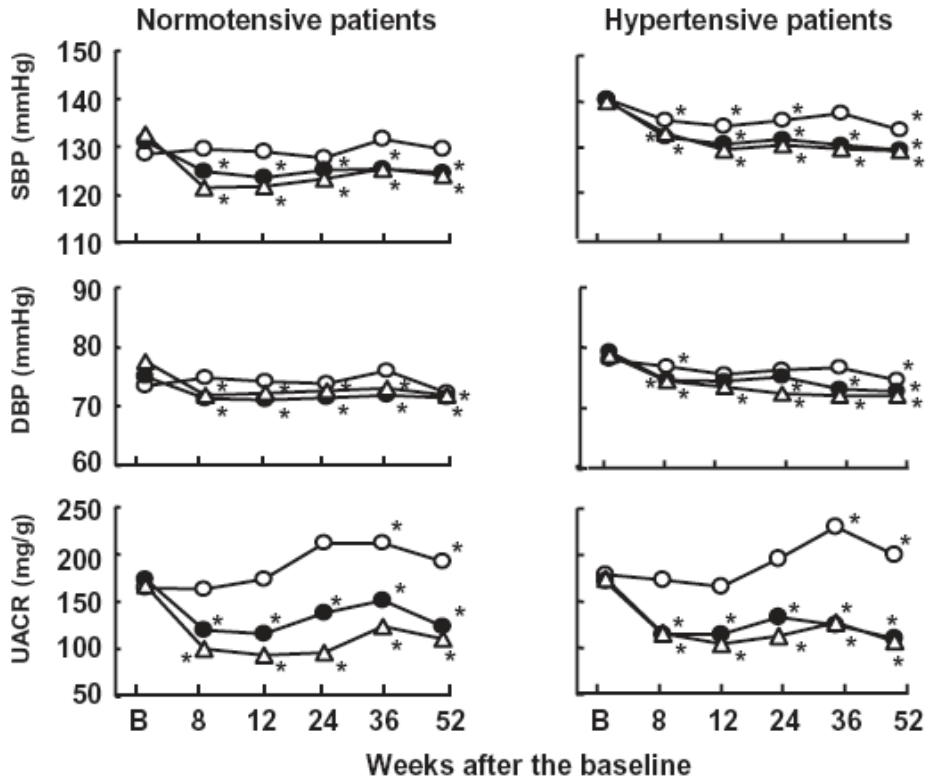

Fig. 1. *Time courses of SBP, DBP, and UACR from baseline to 52 weeks. Each data point indicates a mean value (SD). *Statistical difference from the baseline value at $p < 0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio. Open circle: placebo group; closed circle: telmisartan 40 mg group; open triangle: telmisartan 80 mg group.*

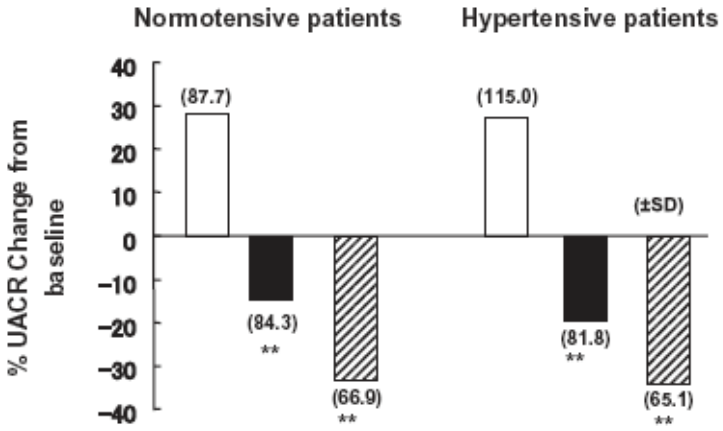

Fig. 2. *Effect of telmisartan on UACR at last observation from baseline. Each data point indicates a mean value (SD). **Statistical difference from placebo group at $p < 0.001$. UACR, urinary albumin-to-creatinine ratio. Open column: placebo group; closed column: telmisartan 40 mg group; hatched column: telmisartan 80 mg group.*

Casas et. al [58] assessed blood-pressure-independent renoprotection with use of ACE inhibitors or ARBs by meta-analyzing 127 trials (N = 73,514) that investigated the effect of different classes of antihypertensive drugs on progression of renal disease, comparing outcomes of trials using placebo controls and trials using active comparator drugs. Out of 150 comparison groups, 99 included only patients with diabetes (weighted mean GFR 84.5 mL/min). Even though this systematic review and meta-analysis was large in scope, it followed a rigorous methodology in search strategy and study selection, as well as statistical analysis providing appropriate summary estimates and outcome measures calculated. It is plausible that there are unidentifiable biases as specific study information and raw data from the studies, and information on the homogeneity or heterogeneity of patient characteristics are not reported. It is notable that the authors do not report biases or limitations, but do report that they did not have binding ties to a funding source.

Excerpt begins.

> In trials that compared the effect of ACE inhibitors or ARBs on the occurrence of end-stage renal disease with the effect of other antihypertensives, no significant benefit of ACE inhibitors or ARBs over other antihypertensive drugs was seen in patients with diabetes (four trials, n = 14,437; Figure 2A). In trials that compared the effect of ACE inhibitors or ARBs with active comparators on the doubling of creatinine, in patients with diabetes (six trials, n = 3,044), ACE inhibitors or ARBs showed no benefit compared with other antihypertensive drugs (RR = 1.09, 95% CI: 0.55 to 2.15). In trials that compared the effect of ACE inhibitors or ARBs on serum creatinine concentration with that of other antihypertensives In patients with diabetes, no benefit on creatinine was seen (Figure 3A). In trials that compared the effect of ACE inhibitors or ARBs on urine albumin excretion with other antihypertensive drugs, in patients with diabetes, a small reduction in daily urine albumin excretion was seen (Figure 3B). In trials that compared the effect of ACE inhibitors or ARBs with other antihypertensive drugs on the GFR, the GFR did not improve in patients with diabetes (Figure 3C).
>
> In trials with the comparator arm as placebo rather than another antihypertensive drug, patients randomly assigned to receive ACE inhibitors or ARBs were at lower risk of end-stage renal disease and doubling of creatinine, than was placebo (Webtable 1), and also showed reductions in serum creatinine and urine albumin excretion (Webtable 2) Similar benefits were seen in patients with diabetes…Indeed, when blood-pressure differences were reduced substantially by antihypertensive treatment in control groups, there was no evidence of a significant salutary effect of ACE inhibitors or ARBs on renal outcomes in patients with diabetes.

Excerpt Ends.

Figure 2A

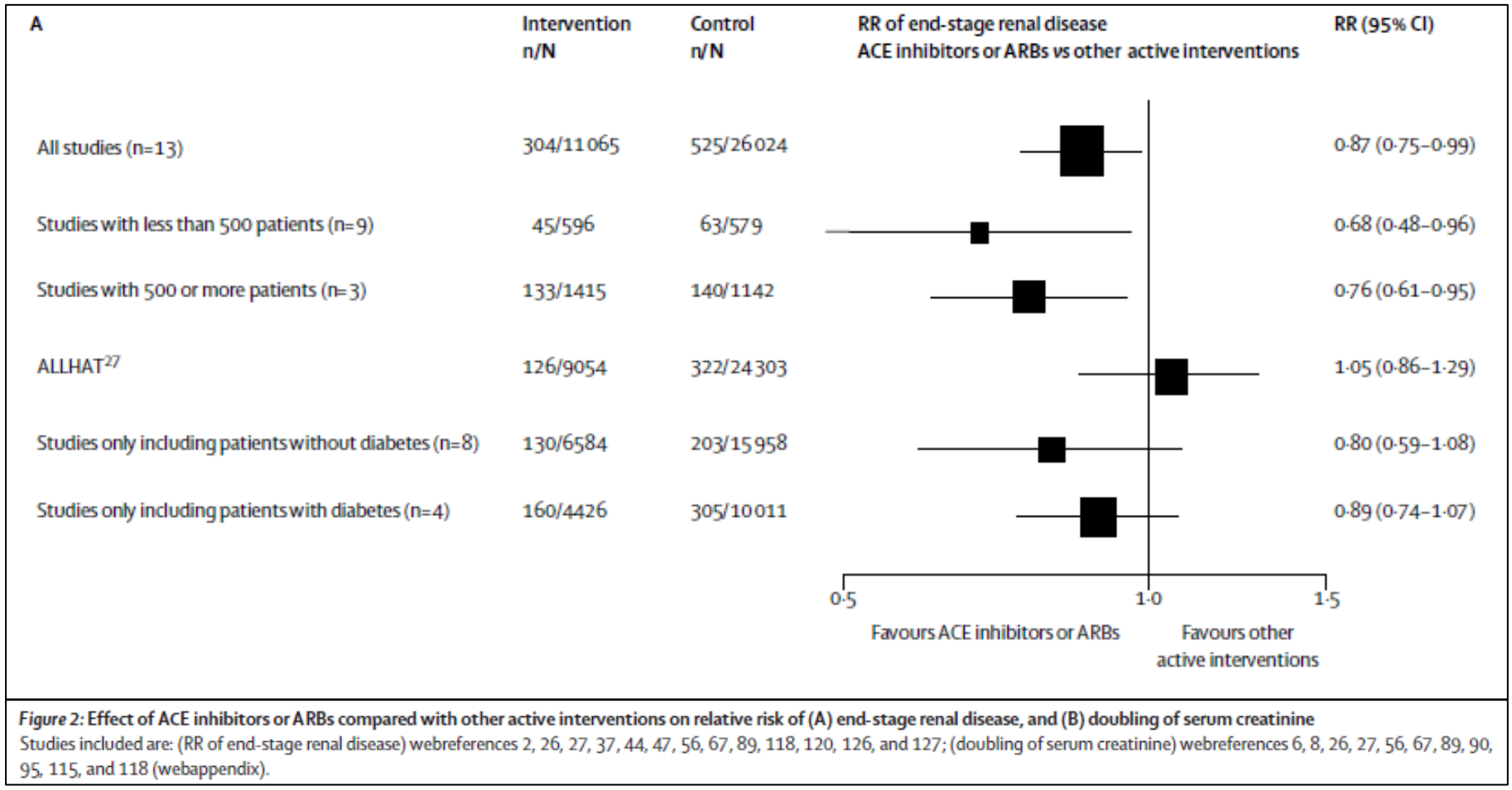

Figure 2: **Effect of ACE inhibitors or ARBs compared with other active interventions on relative risk of (A) end-stage renal disease, and (B) doubling of serum creatinine**
Studies included are: (RR of end-stage renal disease) webreferences 2, 26, 27, 37, 44, 47, 56, 67, 89, 118, 120, 126, and 127; (doubling of serum creatinine) webreferences 6, 8, 26, 27, 56, 67, 89, 90, 95, 115, and 118 (webappendix).

Figure 2B

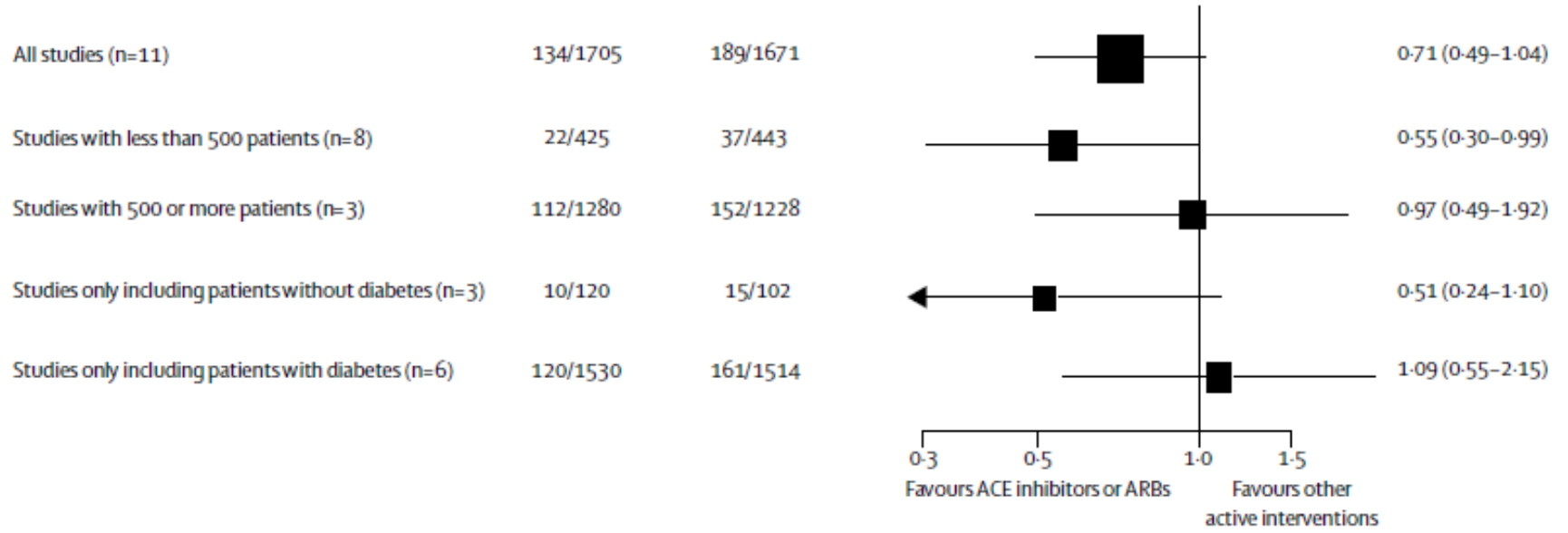

Figure 2: **Effect of ACE inhibitors or ARBs compared with other active interventions on relative risk of (A) end-stage renal disease, and (B) doubling of serum creatinine**
Studies included are: (RR of end-stage renal disease) webreferences 2, 26, 27, 37, 44, 47, 56, 67, 89, 118, 120, 126, and 127; (doubling of serum creatinine) webreferences 6, 8, 26, 27, 56, 67, 89, 90, 95, 115, and 118 (webappendix).

Figure 3A

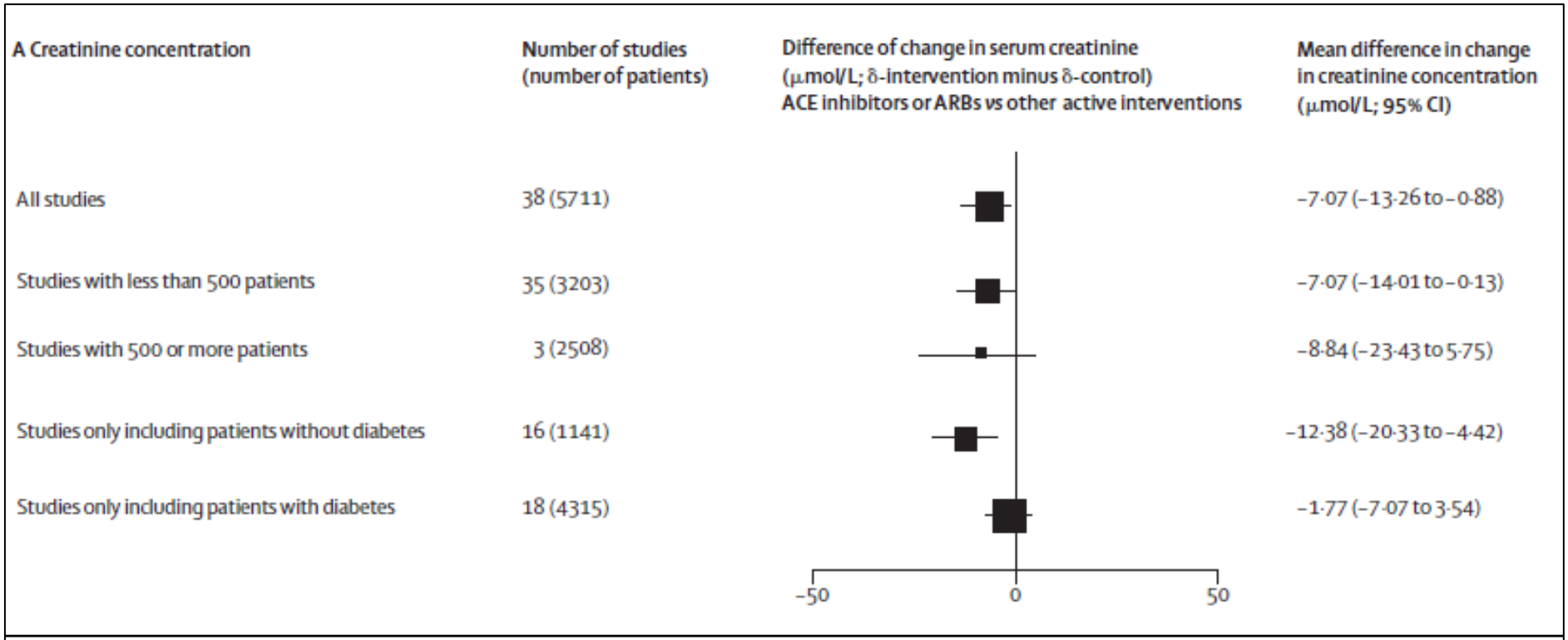

Figure 3: **Effect of ACE inhibitors or ARBs compared with other active interventions on (A) creatinine concentration, (B) urine albumin excretion, and (C) GFR***

Negative values in forest plots indicate a greater reduction in the continuous marker in favour of the ACE-inhibitor or ARB group. Studies included are: (creatinine concentration) webreferences 1, 6, 23, 24, 27, 29, 32, 33, 35, 40, 44, 47, 52, 56, 60, 63, 65, 67, 68, 70, 78, 89, 90, 93, 95, 102, 106–110, 115, 116, 118, 119, 125; (urine albumin excretion) webreferences 1, 6, 11, 15–18, 23, 24, 29, 32, 35, 39, 40, 41, 43, 47, 53, 54, 59, 63, 65, 73, 76, 78, 83, 89, 93, 94, 95, 97, 99, 102, 104, 110, 111, 113, 115, 116, 118, 121, 122; and (GFR) webreferences 1, 2, 5, 6, 7, 8, 11, 12, 15–18, 23, 24, 27, 29, 32, 33, 35–37, 39–41, 43, 46, 47, 49, 52, 55, 56, 59, 63, 65, 68, 76, 78, 83, 88, 90, 93–95, 97, 99, 102, 104, 105, 107, 110, 111, 113, 115, 119–121, 126, 127 (webappendix). *For this group, results from the ALLHAT trial were obtained as a weighted mean by subtracting the results in the diabetes group from the overall study (webreference 127, webappendix).

Figure 3B

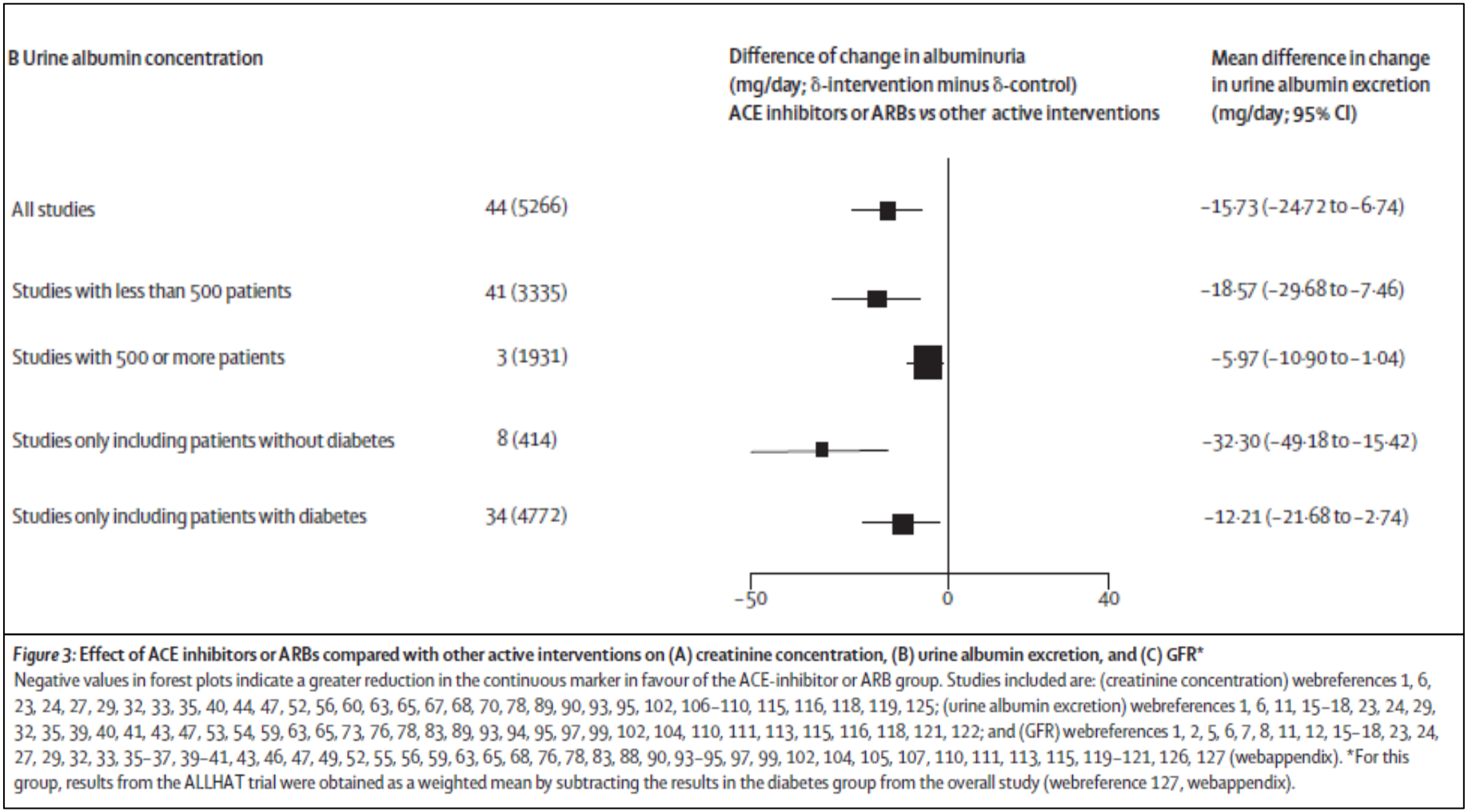

Figure 3: **Effect of ACE inhibitors or ARBs compared with other active interventions on (A) creatinine concentration, (B) urine albumin excretion, and (C) GFR***

Negative values in forest plots indicate a greater reduction in the continuous marker in favour of the ACE-inhibitor or ARB group. Studies included are: (creatinine concentration) webreferences 1, 6, 23, 24, 27, 29, 32, 33, 35, 40, 44, 47, 52, 56, 60, 63, 65, 67, 68, 70, 78, 89, 90, 93, 95, 102, 106–110, 115, 116, 118, 119, 125; (urine albumin excretion) webreferences 1, 6, 11, 15–18, 23, 24, 29, 32, 35, 39, 40, 41, 43, 47, 53, 54, 59, 63, 65, 73, 76, 78, 83, 89, 93, 94, 95, 97, 99, 102, 104, 110, 111, 113, 115, 116, 118, 121, 122; and (GFR) webreferences 1, 2, 5, 6, 7, 8, 11, 12, 15–18, 23, 24, 27, 29, 32, 33, 35–37, 39–41, 43, 46, 47, 49, 52, 55, 56, 59, 63, 65, 68, 76, 78, 83, 88, 90, 93–95, 97, 99, 102, 104, 105, 107, 110, 111, 113, 115, 119–121, 126, 127 (webappendix). *For this group, results from the ALLHAT trial were obtained as a weighted mean by subtracting the results in the diabetes group from the overall study (webreference 127, webappendix).

Figure 3C

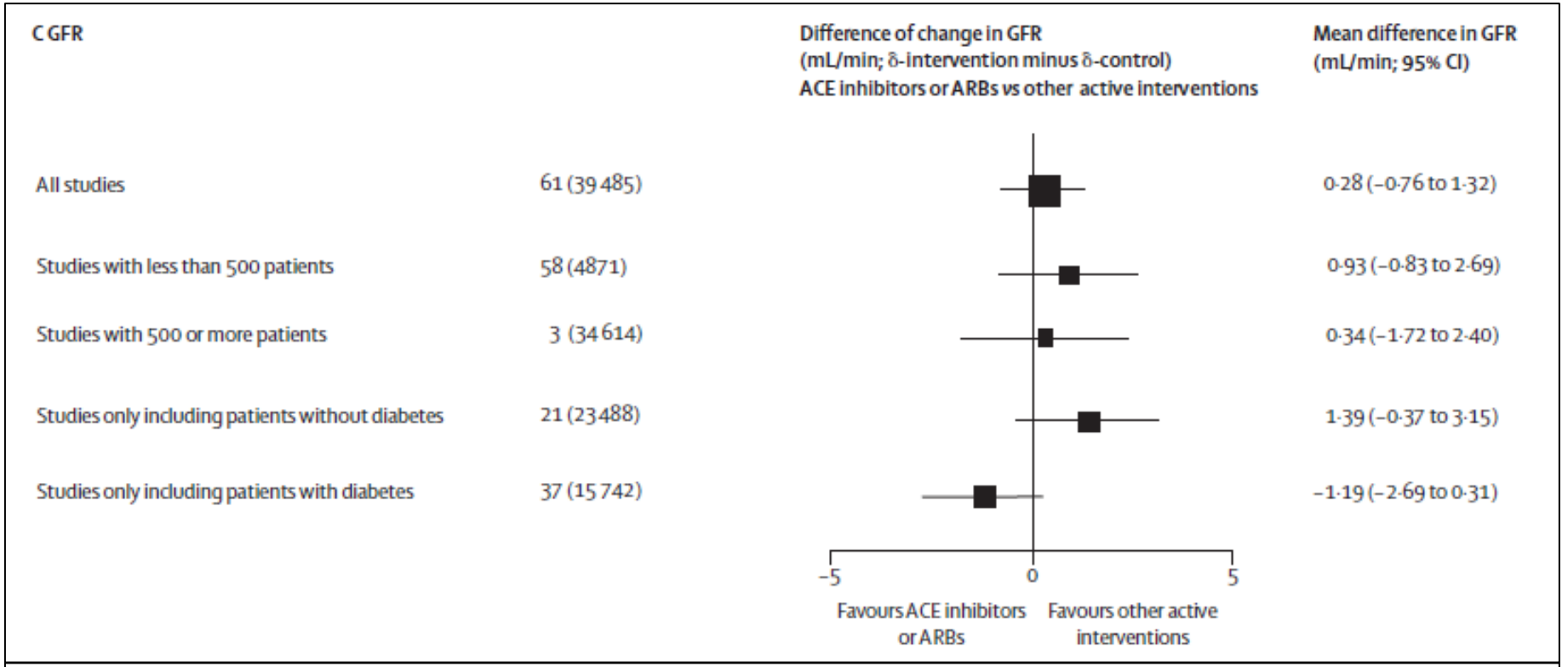

Figure 3: **Effect of ACE inhibitors or ARBs compared with other active interventions on (A) creatinine concentration, (B) urine albumin excretion, and (C) GFR***

Negative values in forest plots indicate a greater reduction in the continuous marker in favour of the ACE-inhibitor or ARB group. Studies included are: (creatinine concentration) webreferences 1, 6, 23, 24, 27, 29, 32, 33, 35, 40, 44, 47, 52, 56, 60, 63, 65, 67, 68, 70, 78, 89, 90, 93, 95, 102, 106–110, 115, 116, 118, 119, 125; (urine albumin excretion) webreferences 1, 6, 11, 15–18, 23, 24, 29, 32, 35, 39, 40, 41, 43, 47, 53, 54, 59, 63, 65, 73, 76, 78, 83, 89, 93, 94, 95, 97, 99, 102, 104, 110, 111, 113, 115, 116, 118, 121, 122; and (GFR) webreferences 1, 2, 5, 6, 7, 8, 11, 12, 15–18, 23, 24, 27, 29, 32, 33, 35–37, 39–41, 43, 46, 47, 49, 52, 55, 56, 59, 63, 65, 68, 76, 78, 83, 88, 90, 93–95, 97, 99, 102, 104, 105, 107, 110, 111, 113, 115, 119–121, 126, 127 (webappendix). *For this group, results from the ALLHAT trial were obtained as a weighted mean by subtracting the results in the diabetes group from the overall study (webreference 127, webappendix).

Figure 4A

A

Degree of change of systolic blood pressure Mean difference (95% CI)	ACE inhibitors/ARB (n/N)	Other active interventions (n/N)	RR of end-stage renal disease in clinical trials using ACE inhibitors or ARBs vs other interventions	RR (95% CI)
−6·9 mm Hg (−9·1 to −4·8)	117/1346	155/1291		0·74 (0·59 to 0·92)
−1·6 mm Hg (−2·8 to −0·4)	273/6344	356/6327		0·77 (0·67 to 0·89)
1·5 mm Hg (0·1 to 2·9)	206/11049	397/26 043		0·90 (0·72 to 1·12)

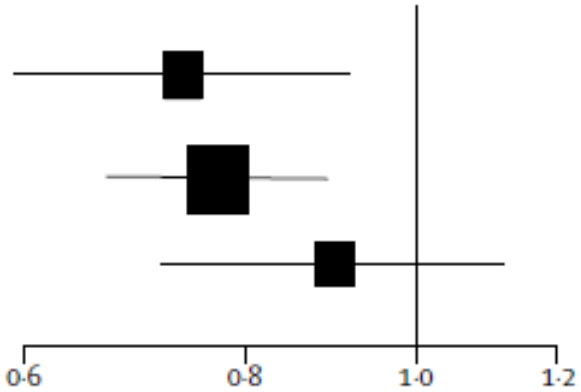

Figure 4: Stratified effect of ACE inhibitors or ARBs on (A) RR of end-stage renal disease and (B) urine albumin excretion, according to difference achieved in systolic blood pressure between randomised groups

Data on these figures include information from placebo-controlled trials and trials with active interventions.

Figure 4B

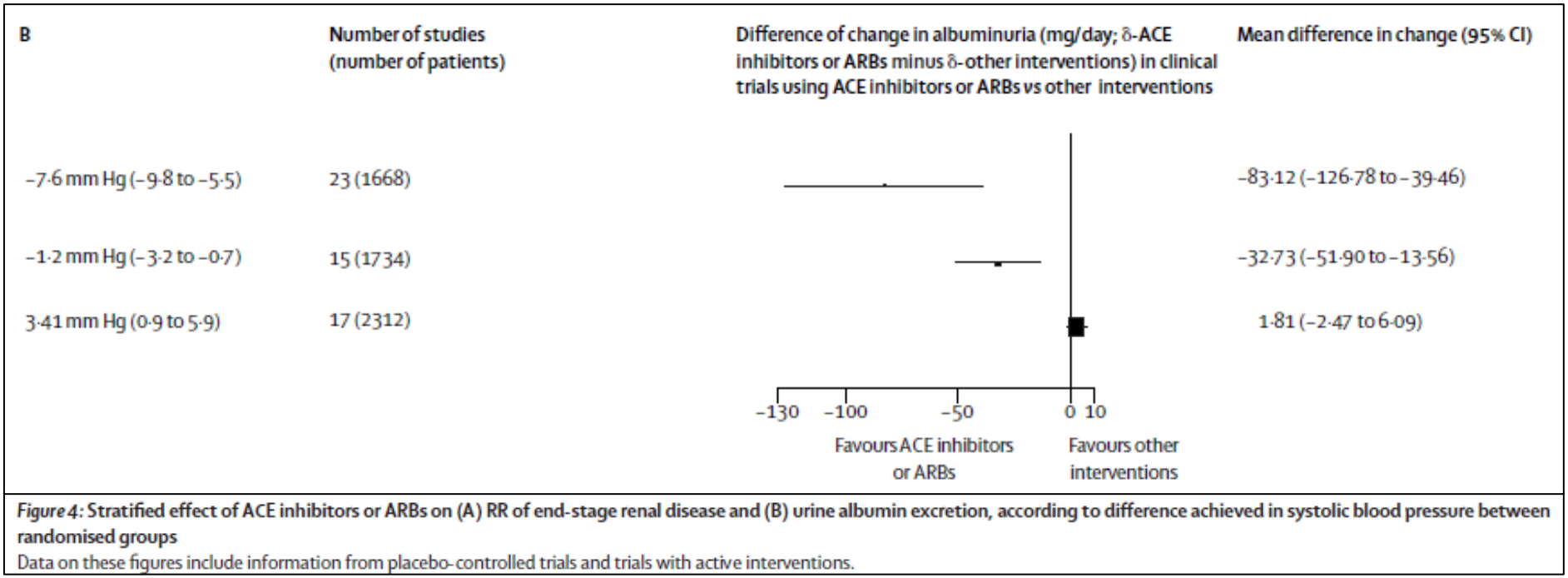

Figure 4: **Stratified effect of ACE inhibitors or ARBs on (A) RR of end-stage renal disease and (B) urine albumin excretion, according to difference achieved in systolic blood pressure between randomised groups**

Data on these figures include information from placebo-controlled trials and trials with active interventions.

Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis

	Number of ACE-inhibitor or ARB events (total)	Control events (total)	RR (95% CI)	Mean difference in change in systolic blood pressure (95% CI)
Doubling of serum creatinine				
All studies (n=10)	420 (6568)	562 (6514)	0·71 (0·57 to 0·88)	−2·27 (−4·02 to −0·52)
Studies with less than 500 patients (n=4)	36 (386)	77 (362)	0·47 (0·31 to 0·71)	−0·46 (−5·8 to 4·9)
Studies with 500 patients or more (n=6)	384 (6182)	485 (6152)	0·79 (0·65 to 0·97)	−2·51 (−4·6 to −0·4)
Studies only including patients without diabetes (n=1)	7 (78)	20 (88)	0·40 (0·17 to 0·88)	−1·0 (−12·1 to 10·1)
Studies only including patients with diabetes (n=8)	383 (6190)	486 (6143)	0·78 (0·63 to 0·95)	−1·74 (−3·2 to −0·2)
End-stage renal disease				
All studies (n=9)	304 (6301)	403 (6263)	0·75 (0·66 to 0·86)	−2·69 (−4·51 to −0·88)
Studies with less than 500 patients (n=4)	53 (420)	87 (411)	0·61 (0·45 to 0·84)	−0·71 (−6·1 to 4·6)
Studies with 500 patients or more (n=5)	251 (5881)	316 (5852)	0·79 (0·68 to 0·92)	−3·03 (−5·1 to −0·8)
Studies only including patients without diabetes (n=3)	33 (213)	56 (209)	0·61 (0·41 to 0·88)	−3·62 (−12·4 to 5·2)
Studies only including patients with diabetes (n=5)	270 (5788)	346 (5771)	0·79 (0·67 to 0·90)	−2·01 (−3·6 to −0·4)

Studies included for doubling of serum creatinine are in webreferences 20, 42, 50, 57, 66, 67, 72, 74, 92, and 95, and those for end-stage renal disease in webreferences 20, 42, 50, 51, 66, 67, 72, 74, and 96 (webappendix). The Egger test for studies investigating the doubling of serum creatinine was p=0·25, and for those investigating ESRD was p=0·77.

Webtable 1: **Effects on renal endpoints of placebo-controlled trials with ACE inhibitors or ARBs**

Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis

	Number of trials (number of patients)	Mean difference in change of surrogate markers (95% CI)*	Mean difference in change in systolic blood pressure, mm Hg (95% CI)*	Egger test (p)
Creatinine (μmol/L)				
All studies	13 (11 339)	−11·49 (−19·01 to −3·98)	−2·52 (−3·9 to −1·10)	0·07
Studies with less than 500 patients	9 (1119)	−14·14 (−26·96 to −3·09)	−1·47 (−3·9 to 0·98)	..
Studies with 500 patients or more	4 (10 220)	−8·84 (−18·56 to 0·88)	−3·63 (−6·3 to −1·0)	..
Studies only including patients without diabetes	1 (166)	−45·97 (−125·08 to 33·15)	−1·0 (−12·1 to 10·1)	..
Studies only including patients with diabetes	11 (10 590)	−12·38 (−20·77 to −3·98)	−1·97 (−3·1 to −0·79)	..
Albuminuria (mg/day)				
All studies	29 (2852)	−83·01 (−112·1 to −53·93)	−5·96 (−9·05 to −2·86)	0·006
Studies with less than 500 patients	27 (1732)	−95·87 (−142·72 to −49·02)	−5·96 (−9·05 to −2·86)	..
Studies with 500 patients or more	2 (1120)	−26·92 (−38·8 to −15·04)	..	..
Studies only including patients without diabetes	..	..	..	..
Studies only including patients with diabetes	29 (2852)	−83·01 (−112·1 to −53·93)	−5·96 (−9·05 to −2·86)	..
GFR (mL/min)				
All studies	34 (6727)	1·22 (−0·95 to 3·39)	−4·41 (−6·57 to −2·25)	0·91
Studies with less than 500 patients	32 (2560)	3·55 (0·57 to 6·53)	−5·04 (−7·6 to −2·5)	..
Studies with 500 patients or more	2 (4167)	−1·37 (−4·51 to 1·77)	−2·45 (−5·0 to 0·1)	..
Studies only including patients without diabetes	4 (436)	2·51 (−4·12 to 9·14)	−4·39 (−12·9 to 4·1)	..
Studies only including patients with diabetes	30 (6291)	1·07 (−1·25 to 3·39)	−4·58 (−6·9 to −2·2)	..

List of studies included for every outcome are: (creatinine) webreferences 3, 4, 29, 42, 50, 57, 61, 66, 67, 72, 74, 82, and 92; (albuminuria) webreferences 3, 4, 10, 17, 19, 21, 22, 25, 29, 38, 45, 53, 54, 57, 64, 71, 75, 77, 79, 80, 85–87, 91, 92, 100, 101, and 114; (GFR) webreferences 3, 4, 10, 14, 17, 19, 21, 25, 28, 29, 36, 42, 45, 50, 51, 57, 61, 64, 66, 71, 75, 77, 79, 82, 85, 86, 87, 88, 91, 96, 100, 101, and 124 (webappendix). The Egger test was only calculated when all studies were combined. *Calculated as δ-experimental minus δ-reference, as described in methods section.

Webtable 2: Effects on continuous renal markers of placebo-controlled trials with ACE inhibitors or ARBs

Table 4: Characteristics of studies in meta-analysis

	Number of group comparisons (number of patients)	Mean (range) sample size	Mean proportion of patients with hypertension (range)	Proportion of studies only including patients with diabetes (%)	Mean (range) baseline GFR (mL/min)	Mean (range) baseline creatinine (μmol/L)	Mean (range) baseline albuminuria (mg/day)
Group comparisons							
All	150 (73 514)	490 (11–33 357)	64·9 (0–100)	73%	86·9 (15·8–184·2)	113·1 (68–389)	602·8 (7·2–3100)
ACE inhibitors or ARBs *vs* placebo	48 (16 588)	345 (11–4912)	32·6 (0–100)	89%	97·8 (15·8–184·2)	110·5 (69·8–389)	535·5 (7·3–1900)
ACE inhibitors or ARBs *vs* other active interventions	77 (43 439)	564 (13–33 357)	85·7 (0–100)	62%	77·4 (18·8–150)	127·0 (68–349·2)	519·5 (7·2–3000)
ACE inhibitors *vs* ARBs	5 (594)	118 (24–250)	75 (0–100)	60%	80·3 (38·4–96·7)	157·3 (70·7–265·2)	92·6 (92–102)
Other active interventions *vs* placebo	11 (6390)	581 (12–4406)	40 (0–100)	89%	99·5 (64·1–129)	98·4 (78·6–149·4)	1128·7 (7·3–1900)
Other active interventions *vs* other active interventions	9 (6503)	722 (20–6125)	100 (0–100)	75%	76·1 (55·8–98)	141·4 (120·2–152)	950·5 (55–3100)

*American Diabetes Association: Standards of Medical Care in Diabetes—2009**

Excerpt starts.

Recommendation:

- To reduce the risk or slow the progression of nephropathy, optimize glucose control. (A)
- To reduce the risk or slow the progression of nephropathy, optimize blood pressure control. (A)
- In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. (A)

Evidence Grade A: Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including: evidence from a well-conducted multicenter trial; evidence from a meta-analysis that incorporated quality ratings in the analysis; Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at Oxford. Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including: evidence from a well-conducted trial at one or more institutions; evidence from a meta-analysis that incorporated quality ratings in the analysis.

Rationale:

Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro- to macroalbuminuria in patients with type 1 and type 2 diabetes. The UKPDS provided strong evidence that control of blood pressure can reduce the development of nephropathy. In addition, large prospective randomized studies in patients with type 1 diabetes have demonstrated that achievement of lower levels of systolic blood pressure (< 140 mmHg) resulting from treatment using ACE inhibitors provides a selective benefit over other antihypertensive drug classes in delaying the progression from micro- to macroalbuminuria and can slow the decline in GFR in patients with macroalbuminuria. In type 2 diabetes with hypertension and normoalbuminuria, ACE inhibition has been demonstrated to delay progression to microalbuminuria.

In addition, ACE inhibitors have been shown to reduce major CVD outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes, thus further supporting the use of these agents in patients with microalbuminuria, a CVD risk factor. ARBs have also been shown to reduce the rate of progression from micro- to macro-albuminuria as well as ESRD in patients with type 2 diabetes. Some evidence suggests that ARBs have a smaller magnitude of rise in potassium compared with ACE inhibitors in people with nephropathy. It is important to note that the benefits of both ACE inhibitors and ARBs in those with diabetic nephropathy are strongly associated with the reduction in albuminuria.

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* For an explanation of the letter grading in this excerpt, please see Appendix C.

Combinations of drugs that block the rennin- angiotensin-aldosterone system (e.g., an ACE inhibitor plus an ARB, a mineralocorticoid antagonist, or a direct rennin inhibitor) have been shown to provide additional lowering of albuminuria. However, the long-term effects of such combinations on renal or cardiovascular outcomes have not yet been evaluated in clinical trials.

Other drugs, such as diuretics, calcium channel blockers, and beta-blockers, should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs or as alternate therapy in the rare individual unable to tolerate ACE inhibitors or ARBs.

Studies in patients with varying stages of nephropathy have shown that protein restriction helps slow the progression of albuminuria, GFR decline, and occurrence of ESRD. Protein restriction should be considered particularly in patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control and use of ACE inhibitor and/or ARBs.

Excerpt ends.

2007 Update:

No new evidence was found, the recommendation remains unchanged.

2005 Update:

- One RCT[59] (n = 250) was identified in which no significant difference was found in change in glomerular filtration rate, mortality, stroke, heart failure, or myocardial infarction between an angiotensin II receptor blocker and an ACE inhibitor in people with type 2 diabetes and early nephropathy.

Definitions of microalbuminuria and clinical albuminuria as defined by the ADA and National Kidney Foundation:[21, 47]

Category	24-h collection (mg/24-h)	Timed Collection (mcg/min)	Spot Collection (mcg/mg creatinine)
Microalbuminuria	30 to 300	20 to 200	30 to 300
Albuminuria	> 300	> 200	> 300

- Two systematic reviews were found that looked at the effect of ACE inhibitors on intermediate outcomes in patients with diabetes and microalbuminuria who had normal blood pressure.[60, 61] There are no high-quality published studies that provide health outcomes, such as ESRD and death, for treatment of normotensive people with diabetes and microalbuminuria.
- The Cochrane systematic review included 13 RCTs and one meta-analysis that compared ACE inhibitors (captopril, enalapril, and lisinopril) to placebo in normotensive people with type 1 or type 2 diabetes and microalbuminuria or albuminuria.[60] The mean age of the participants ranged from 32 to 48 years old.
  - All of the RCTs were relatively small (study size ranged from 15 to 143 participants) and each trial lasted more than a year.
  - The authors found a small, but significant effect of ACE inhibitors on GHb (gylcosylated hemoglobin). All three types of ACE inhibitors significantly reduced albumin excretion rate when compared with placebo.

  - Albumin rate increased in the placebo group 11.8% (95% CI: -3.3 to 29.1; p = ns) and decreased with an ACE inhibitor (captopril) 17.9% (95% CI: -29.6 to -4.3; p = 0.004). ACE inhibitor (enalapril) was also associated with an absolute risk reduction of 42% (95% CI: 15 to 69); p not stated) for nephropathy over seven years.
- The second systematic review only included studies that enrolled normotensive patients with type 1 diabetes and microalbuminuria.[61] Twelve RCTs were included in this systematic review.
  - The RCTs were relatively small and ranged from 16 to 137 participants. The age range was 17 to 70 years old and the duration of the trials varied from one to four years.
  - ACE inhibitors (captopril, lisinopril, enalapril, perindopril, and ramipril) were compared with placebo.
  - Albumin excretion rates were 50.5% lower (95% CI: 29.2 to 65.5; $p < 0.001$) with ACE inhibitors compared with placebo at two years. A decrease in progression to albuminuria was associated with ACE inhibitors (OR = 0.38; 95% CI: 0.25 to 0.57; $p < 0.001$). More patients regressed to normoalbuminuria in the treatment groups than the control groups (OR = 3.07; 95% CI: 2.15 to 4.44; $p < 0.001$).
- The GDT recommends ACE inhibitors in people with diabetes and normal blood pressure because of it's positive effect on microalbuminuria. The effect of ACE inhibitors on prevention of renal failure is not yet established.

Other Considerations

- Doubling serum creatinine was found to be associated with increased mortality, dialysis, and kidney transplantation.[54] A statistically significant correlation was found between decreased survival and elevated urinary albumin concentration (microalbuminuria and proteinuria) in people with diabetes. Microalbuminuria is predictive of clinical proteinuria and increased mortality.[55]
- The HOPE study[32] found that an ACE inhibitor (ramipril) reduces urinary protein excretion and reduces cardiovascular morbidity and mortality in older patients with diabetes. The same protective effect was observed in patients without microalbuminuria.
- ACE inhibitors are generally considered to have a "class" effect due to the cardiovascular protective, antihypertensive, and reno-protective properties demonstrated by each ACE inhibitor that has been studied. No studies were found that compare different ACE inhibitors and it is unlikely that any such studies will be conducted in the near future.
- There is no consistent evidence about starting dosage.

13. Lipid Management

13A Statin Therapy: DM and CAD

Statin therapy is recommended for all patients with diabetes and CAD.

13B Statin Therapy: Initial Dose

Initiate statin therapy with at least simvastatin 40 mg daily.*

13C Statin Therapy: Age 40 or Older

Statin therapy is recommended, regardless of baseline LDL-C. NNT = 23†

13D Statin Therapy: Age 39 or Under

For people with diabetes under age 39 or younger WITH > 1 risk factor:‡

- Statin therapy is RECOMMENDED when LDL-C > 100 mg/dL.
- Statin therapy is OPTIONAL when LDL-C < 100 mg/dL.

For people with diabetes under age 39 or younger WITHOUT risk factors:‡

- Statin therapy is RECOMMENDED when LDL-C > 130 mg/dL.
- Statin therapy is OPTIONAL when LDL-C < 130 mg/dL.

Rationale:

Evidence for Recommendation 13A: Good

2009 Update:

These recommendations are excerpted from the 2008 KP National Dyslipidemia Management in Adults Clinical Practice Guidelines. KP National is working towards complete alignment and integration of recommendations among the Diabetes, CAD, Hypertension and Dyslipidemia Guidelines, under the oversight of the Integrated Cardiovascular Health Leads (John Merenich, MD, Marc Jaffe, MD, Jim Dudl MD, John Golden MD, Joel Handler MD, and Wiley Chan MD). The first step in this process is to align the mostly minor discrepancies between the existing recommendations that address the same topic. The Diabetes Guideline had several recommendations that had been updated by the other GDTs, and the ICVH Leads felt that it would be best to formally adopt those updated recommendations in the Diabetes Guideline.

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

The following rationale and accompanying recommendations are adopted from the Kaiser Permanente National Dyslipidemia Guidelines. (http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html)

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* Lower doses recommended for patients at high risk for rhabdomyolysis.

† For every 23 diabetics or people with coronary disease, aged 40 to 80 years, who are treated with 40 mg of simvastatin daily, for fi ve years, one mortality or fatal or non-fatal vascular event will be prevented.

‡ Risk factors include: duration of diabetes > 10 years, HDL-C < 40 mg/dL, current smoker or family history of premature CAD [Clinical CAD or sudden death in a first-degree relative aged < 55 (men) and < 65 (women)] one encounter in the measurement year, regardless of setting, of the following—chronic heart failure (CHF); prior myocardial infarction (MI); chronic renal failure (CRF)/end-stage renal disease (ESRD); dementia; blindness; and/or, amputation.

Although the recommendations of the Kaiser Permanente National Diabetes Guideline (this document) and the KP National Dyslipidemia Guideline are generally consistent with each other, there are a few differences, including:

- The KP National Diabetes Guideline separates guidance for statin therapy into three age categories: age 40 to 80, age < 40, and age > 80 years.
- Like the KP National Dyslipidemia Guideline, the KP National Diabetes Guideline recommends simvastatin for all patients aged 40 to 80 years with diabetes, regardless of baseline LDL. However, the Diabetes Guideline also includes an additional criterion of total cholesterol (TC) > 135 mg/dl.

The following is an excerpt from the KP National Dyslipidemia Guidelines (http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html):

> "There are no head-to-head comparison studies of the efficacy of different statins or statins vs. fibrates, resins, or niacin in reducing CAD events in people with diabetes. Therefore, the choice of drug would be based on a comparison of diabetes mellitus (DM) subgroup analyses and RCTs of individual drug treatments vs. placebo.
>
> ***Lipid-Lowering Trials in Diabetes Mellitus Populations***
>
> One RCT (ASPEN; Knopp et al., 2006[62]) compared atorvastatin 10 mg vs. placebo in 2,410 subjects aged 40-75 with type 2 diabetes. At four years, there were no differences between the groups in the rates of cardiovascular death, nonfatal/silent MI, nonfatal stroke, recanalization, CABG, resuscitated cardiac arrest, or hospitalization due to worsening angina. It should be noted that the study population featured a mix of primary and secondary prevention populations, and subgroup analyses of these populations were not intention-to-treat comparisons. It should also be noted that many study participants were required to discontinue study medication midway in the trial.
>
> ***Lipid-lowering Trials with DM Subgroup Analysis***
>
> "One systematic review [Clinical Evidence, Issue 11, August 2004 (on-line version)] has compared HMG Co-A reductase inhibitors (statins) vs. placebo, and fibrates vs. placebo. Subsequent updates of this review were separated into systematic reviews focusing on dyslipidemia in diabetes (Patel et al., 2006[63]) and the prevention of cardiovascular events in diabetes (Sigal et al., 2006[64]); however, new evidence was not captured in these updates. Additional RCTs were identified that compared statins vs. placebo in people with diabetes.

- "Clinical Evidence reviewed five RCTs of the efficacy of various drug therapies in preventing coronary heart disease events in people with diabetes. Statin and fibrates were compared with placebos for both primary and secondary prevention.

The following summary is excerpted from Clinical Evidence:

Primary Prevention:

"We found no systematic review. We found five large RCTs with significant numbers of people with diabetes comparing lipid lowering agents vs. placebo, and found reductions in the risk of cardiovascular events.

"In the first RCT,[65] men aged 45 to 73 years and women aged 55 to 73 years were randomized to diet plus lovastatin 20 to 40 mg daily or diet plus placebo, and followed for a mean of 5.2 years. Among those with diabetes, no significant difference between lovastatin and placebo in myocardial infarction, unstable angina, or sudden cardiac death over five years (4/84 [4.8%] events with lovastatin vs. 6/71 [8.5%] events with placebo; ARR = +3.7%; 95% CI: -5.6% to +11.9%; RR = 0.56, 95% CI: 0.16 to 1.91).

"The second RCT[66] that included 4,081 Finnish men aged 40 to 55 years compared gemfibrozil 600 mg twice daily vs. placebo over five years in people with diabetes (cardiovascular events rate: 3.4% vs. 10.5%; RR = 0.33).

"The third RCT[67] that included 164 men and women with type 2 diabetes, aged 35 to 65 years, compared bezafibrate vs. placebo for three years in people with diabetes (cardiovascular events rate: 7.8% vs. 25%; RR = 0.31).

"A diabetic subgroup analysis from a fourth RCT[29] found, "…no significant difference in cardiac death or non-fatal myocardial infarction between pravastatin 40 mg and placebo over 4.8 years (one RCT 3,638 people aged 55 years with type 2 diabetes and additional CAD risk factors; CAD death plus non-fatal myocardial infarction: RR = 0.89; (95% CI: 0.71 to 1.10)." It is possible that the unblinded design of this study may have resulted in a bias of the observed study results. The overall relative risk for this trial was not statistically significantly different from that of this subgroup.

"A fifth RCT,[68] found no significant difference in cardiovascular death or myocardial infarction between atorvastatin 10 mg daily and placebo over three years (n = 2,532 people aged 40 to 79 years with diabetes, hypertension, total cholesterol > 6.5 mmol/L (251 mg/dL) and at least two other cardiovascular risk factors but without coronary artery disease diagnosis; CAD death or myocardial infarction: RR = 0.84 (95% CI: 0.55 to 1.29). With regard to the results of this study, Clinical Evidence states that the ASCOT-LLA trial was, "…terminated early due to high efficacy of atorvastatin in the overall study population (HR for cardiovascular death plus non-fatal myocardial infarction 0.64; 95% CI: 0.05 to 0.083). Although the difference was not significant in the diabetic subgroup, the confidence intervals for diabetic and non-diabetic subgroups overlapped one another." A subsequent reanalysis of these data (Server et al., 2005[69]) found that atorvastatin was associated with a significantly reduced risk of a composite measure of total cardiovascular events and procedures in the 2,226 diabetic study subjects without prior CVD (HR = 0.75, 95% CI: 0.57 to 0.99)

"In a primary prevention subgroup analysis of diabetes mellitus patients from the Heart Protection Study, 2,913 out of the 5,963 diabetic patients had no prior atherosclerotic disease.

"With a mean baseline LDL of 124 mg/dL, simvastatin 40 mg produced a 30% fall in LDL in the DM population.

"In DM patients with no vascular disease, the relative risks of a new vascular event (total CAD or total stroke or revascular-ization) with treatment (vs. placebo) were as follows:

ARR = 4.4%
RRR = 34%
P < 0.0001
NNT = 23

"For the entire diabetes subgroup:

Simvastatin reduced major vascular events by approximately one-third
NNT = 14

"These results provide support for the recommendation to treat all diabetic patients regardless of baseline LDL.

"A sixth RCT [70] published subsequent to the Clinical Evidence review compared treatment with atorvastatin 10 mg to placebo in patients (n = 2,838, age 40 to 75) with type 2 diabetes, no history of CVD and LDL levels > 160 mg/dL. Patients in the atorvastatin group experienced a 3.2% absolute risk reduction in the primary end point of acute coronary events, revascularization or stroke (event rate: 5.8% atorvastatin vs. 9.0% placebo, ARR = 3.2%, NNT = 31 patients over four years, p = 0.001). This trial supports the recommendation to treat all patients with diabetes regardless of baseline LDL."

"From the available subgroup data for primary prevention in diabetics, when compared to placebo, fibrates, in some cases, appeared to be more effective than statins in lowering cardiovascular event rates. However, 95% CI and p values were not reported. It is uncertain whether the reported results reached statistical significance for primary prevention trials.

The following summary is excerpted from Clinical Evidence:

Secondary Prevention:
"We found one systematic review and six RCTs that included people with diabetes. A systematic review by Huang, et el., 2001, reviewed three RCTs (4S, LIPID, CARE) and found that pravastatin or simvastatin significantly reduced cardiovascular events over six years compared with placebo (n = 1,570 people: 43 events per 1,000 person year with statins vs. 44 events with placebo per 1,000 person years; RR = 0.77 (95% CI: 0.62 to 0.96).

The three trials are further summarized below:
"One RCT [71] that included 4,444 men and women aged 35 to 70 year…compared simvastatin vs. placebo over a median of 5.4 years…
The relative risk of main end points in a subset of 483 people with diabetes treated with simvastatin were as follows:

Total mortality 0.57 (95% CI: 0.30 to 1.08); not statistically significant;
Major cardiovascular events 0.45 (95% CI: 0.27 to 0.74); statistically significant;
Any atherosclerotic event 0.63 (95% CI: 0.43 to 0.92); statistically significant.

"The second RCT (CARE, 1996) that included 4,159 men and women aged 21 to 75 years compared … pravastatin 40 mg daily vs. placebo over a median of five years. Among the 586 people with diabetes, the relative risk of major coronary events (death from coronary disease, non-fatal acute myocardial infarction (AMI), coronary artery bypass graft, or PTCA) was 0.75 (95% CI: 0.57 to 1.0); barely statistically significant.

"The third RCT (LIPID, 1998[72]) that included 9,014 men and women aged 31 to 75 years compared … pravastatin 40 mg daily vs. placebo for a mean of 6.1 years. Among the 782 participants with diabetes, the relative risk of coronary heart disease death or non-fatal AMI was 0.84 (95% CI: 0.59 to 1.10); non-statistically significant. A subsequent re-analysis (Keech, 2003[73]) of these data expanded the subsample of interest to include "probable" diabetics (based on fasting glucose level), for a total N = 1,077. In this analysis, the reduction in risk of a major CHD event attributable to pravastatin was not statistically significant among study diabetics (RRR = 19%, p = 0.11). Pravastatin reduced the risk of any cardiovascular event by 21% (p < 0.01) and the risk of a stroke by 39% (p < 0.05) among these diabetics.

"A fourth RCT (VA-HIT, 1999) not included in the Huang systematic review included 2,531 men aged > 74 years…and compared gemfibrozil 1,200 mg daily with placebo for a median of 5.1 years (treatment was intended to raise high-density lipoprotein cholesterol (HDL) levels rather than reduce LDL). Among the 627 participants with diabetes, the relative risk of coronary heart disease death or non-fatal AMI was 0.76 (95% CI: 0.57 to 1.0); barely statistically significant.

"A fifth RCT (LIPS, Serruys, et al., 2002) found that fluvastatin significantly reduced cardiac death, non-fatal myocardial infarction, and reintervention over four years compared with placebo (one RCT, 202 people aged 18 to 80 years with diabetes and a diagnosis of CVD: 26/120 [21%] events with fluvastatin vs. 31/82 [37.8%] events with placebo; ARR = 0.161, 95% CI: 0.033 to 0.290; NNT = 7; 95% CI: 4 to 30).

"A diabetic subgroup analysis from a sixth RCT (GREACE, 2003), found that, "…compared with usual care, treatment with atorvastatin to achieve a target LDL of below [< 100 mg/dL] significantly reduced the risk of all cause mortality, non-fatal myocardial infarction, unstable angina, congestive heart failure, revascularization, and stroke over three years (one RCT, 313 people with a diagnosis of CVD, mean age 58 years: RRR = 0.42; p = 0.0001; results presented graphically). The atorvastatin dose was titrated from 10 mg daily to a maximum of 80 mg daily to achieve a target LDL cholesterol of below 2.6 mmol/L [< 100 mg/dL]. Usual care consisted of treatment by the family practitioner, which could include diet, exercise, weight loss and/or drug treatment including lipid lowering agents; 14% of people in the usual care group received any lipid lowering agents."

Mixed Primary and Secondary Prevention:

The following summary is excerpted from Clinical Evidence:

"One RCT (the Diabetes Atherosclerosis Interventions Study, 2001) that included 305 men and 113 women, with mean age 57 years, and with or without CVD diagnosis, compared the effect of fenofibrate 200 mg daily vs. placebo…in type 2 diabetics for a minimum of three years. After 39 months on treatment and six additional months of follow-up, fenofibrate vs. placebo did not significantly reduce the number of patients who either had myocardial infarction or died. [15/207 (7.2%) with fenofibrate vs. 21/211 (9.9%) with placebo; ARR = 2.7%, 95% CI: -2.8% to +8.3%; RR = 0.73, 95% CI: 0.39 to 1.37)]; not statistically significant.
"In the Heart Protection Study (2003) overall results reached statistical significance and further illustrated the effectiveness of statin therapy in people with diabetes (includes people with and without CAD) compared with placebo:

"5,963 out of 20,536 participants, aged 40 to 80, had DM when they enrolled in HPS.

"The following results pertain to the effects of statin on first major vascular event in the DM population with different prior diseases:

DM with prior MI or other CAD: ARR = 4.4%; RRR = 11.6%; NNT = 23; $p < 0.0001$

DM with no prior CAD: ARR = 4.8%; RRR = 25.8%; NNT = 21; $p < 0.0001$

DM with or without prior CAD: ARR = 4.9%; RRR = 19.5%; NNT = 20; $p < 0.0001$

Statins

"In summary, most published clinical trials with sufficient power to detect effects on cardiovascular events have enrolled comparatively few people with diabetes or have excluded them altogether. With the exception of one RCT (CARDS), much of the available evidence is therefore based on subgroup analyses of the larger trials that did include people with diabetes. The available evidence suggested that statins are more effective than fibrates in reducing cardiovascular events when both drugs were compared to placebo. There are currently no published data that compared resins or niacin to placebo in people with diabetes."

End of excerpt.

Overall Conclusion

Based on the Heart Protection Study and in view of these issues, the GDT recommends that all people with diabetes aged 40 years or older be treated, regardless of baseline LDL-C, to an LDL-C goal of < 100 mg/dL. However, the team agreed that the evidence is uncertain with regard to patients who have very low 10-year CAD risk (< 7 to 10%), e.g., some patients with type 1 diabetes, low blood pressure, low LDL-C, and no smoking history. Therefore, clinical judgment is advised when considering lipid-lowering medications in people with diabetes who have very low CAD risk (< 7 to 10%).

14. Lipid Management: LDL Goals

14 An LDL-C goal of < 100 mg/dL, with an optional goal of < 70 mg/dL for people with diabetes and coronary artery disease, but not for people with diabetes without cornonary artery disease.

Rationale:

2009 Update:

This recommendation is excerpted from the 2008 National Dyslipidemia Management in Adults Clinical Practice Guidelines.

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

The following rationale and accompanying recommendations are adopted from the Kaiser Permanente National Dyslipidemia Guidelines (http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html).

While the recommendations between the KP National Diabetes Guidelines and the KP National Dyslipidemia Guidelines are generally consistent, there are a few differences, including:

- The KP National Diabetes Guidelines allow the option of a goal of LDL< 70 for patients with diabetes and CAD.

  The following is an excerpt from the KP National Dyslipidemia Guidelines (http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html):

  "There are no RCTs which explicitly and directly compared the effectiveness of various LDL cut-points for reducing CAD events in patients with diabetes mellitus. A subgroup analysis of diabetics from the Heart Protection Study showed that reducing LDL from 124 mg/dL at baseline to 89 mg/dL over five years was effective for reducing CAD events; however, this study was not designed for the purpose of comparing different target LDL levels. Given the high baseline CAD risk among our "high-risk" groups such as diabetic patients aged 40 or greater, the GDT agreed that an LDL target of > 100 mg/dL would be appropriate for diabetic patients aged 40 or greater. In patients with diabetes and CAD, the group believes a more aggressive LDL target should be an option.

  "Several statin RCTs have demonstrated improved outcomes in patients whose LDL was lowered well below 100 mg/dL. Only acute coronary syndrome (ACS) patients have been shown to have improved outcomes when the LDL was lowered below 70 mg/dL (PROVE-IT TIMI 22 and A to Z trials). Two other trials have shown improved outcomes in a variety of CAD patients when the LDL was lowered below 80 mg/dL (MIRACL, AVERT). Although the trials summarized below compared pre- and post-treatment LDL levels, it is important to note these trials were not explicitly designed to compare one LDL treatment goal vs. another.

  "PROVE-IT (2004)
  - Pre-treatment mean LDL = 106 mg/dL
  - Attained LDL in control group = 95 mg/dL
  - Attained LDL in treatment group = 62 mg/dL
  - Effect on coronary events (any death, MI angina, PTCI, CABG, stroke): Relative Risk Reduction = 15%; p = 0.005
  - Follow-up: 18 months
  - Population: people with established atherosclerosis and who were being treated for secondary prevention of a future CAD event.

"Phase Z of A to Z Trial (2004)

- Pre-treatment mean LDL = 111 mg/dL
- Attained LDL in placebo + simvastatin 20 mg/d group at four months = 124 mg/dL
- Attained LDL in placebo + simvastatin 20 mg/d group at 24 months = 81 mg/dL
- Attained LDL in simvastatin 80 mg/d group at four months = 62 mg/dL
- Attained LDL in simvastatin 80 mg/d group at 24 months = 66 mg/dL
- Effect on coronary events: (MI, cardiac mortality, stroke or readmission of for ACS)
- After four months, no statistically significant differences in primary composite endpoints were found between the high-dose vs. low-dose regimens of simvastatin (ARR = 2.3%, HR = 0.89; 95% CI: 0.76 to 1.04).
- Between months four and 24 the primary endpoint was reduced from 9.3% in the simvastatin 20 mg/d group to 6.8% in the higher dose simvastatin 80 mg/d group (ARR = 2.5%, HR = 0.75; 95% CI: 0.60 to 0.95) (any death, MI angina, PTCI, CABG, stroke): Relative Risk Reduction = 15%; p = 0.005
- Follow-up: 24 months
- Population: people with established acute coronary syndrome and who were being treated for secondary prevention of a future CAD event.

"MIRACL (2001)

- Pre-treatment mean LDL = 124 mg/dL
- Attained LDL in control group = 135 mg/dL
- Attained LDL in treatment group = 72 mg/dL
- Effect on coronary events: RRR = 14.9% and RR = 0.84, 95% CI: 0.70 to 1.00, p = 0.048
- Follow-up: 16 weeks
- Population: people seen during the early period after an acute coronary syndrome.

"AVERT (1999)

- Pre-treatment mean LDL ≥ 115 mg/dL
- Attained LDL in control group = 119 mg/dL
- Attained LDL in treatment group = 77 mg/dL
- Effect on coronary events: Risk Reduction = 36%; p = 0.048
- Follow-up: 18 months
- Population: people with established atherosclerosis and who were being treated for secondary prevention of a future CAD event."

End of excerpt.

Conclusion:

Given that all statins appear to be efficacious for lowering LDL-C, the choice of a drug should be based on cost and evidence of benefit on direct health outcomes. Simvastatin has been shown to be clinically effective for improving direct health outcomes, and since it is available as a generic drug in the formulary, it is significantly less expensive than other statins.

Therefore, simvastain should be used as first-line therapy whenever statins are indicated.

Drug Therapy for Primary and Secondary Prevention of Cardiovascular Events in the General Diabetes Population

15. ACE Inhibitor Therapy for Prevention of Cardiovascular Disease (CVD)

15 The GDT recommends ACE inhibitors therapy for patients with diabetes aged ≥ 55 years with one or more cardiovascular risk factors (total cholesterol > 200 mg/l, HDL cholesterol ≤ 35 mg/l, hypertension, microalbuminuria, or current smoking); or a history of CVD (CAD, stroke, or peripheral vascular disease). *Evidence-based: B*

Rationale:

Evidence for Recommendation 15: Good

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- One large multicenter RCT was found that compared an ACE inhibitor to placebo in the prevention of cardiovascular events.[32]
- 3,577 people with diabetes over age 55 with a history of cardiovascular disease [CAD, stroke, or peripheral vascular disease (PVD)], or diabetes plus at least one other CV risk factor (total cholesterol > 5.2 mmol/l, HDL = 0.9 mmol/l, hypertension, known microalbuminuria, or current smoking) were randomized to either placebo or an ACE inhibitor (10 mg ramipril daily).
- The study ran for 4.5 years and was stopped six months early due to the beneficial effect of ramipril.
- There were significantly fewer MIs in the treatment group (RRR = 22%; 95% CI: 6 to 36; p = 0.01), as well as fewer strokes (RRR = 33%; 95% CI: 10 to 50; p = 0.0074), and CV deaths (RRR = 37%; 95% CI: 21 to 51; p = 0.0001). The relative risk reduction for total mortality with an ACE inhibitor was 24% (95% CI: 8 to 37; p = 0.004).
- There is evidence that an ACE inhibitor can prevent MI, stroke, and mortality in people with diabetes with and without a history of CVD. Intensive therapy lowered the risk of CV disease [HR = 0.46; (95% CI: 0.24 to 0.73)], nephropathy [HR = 0.39; (95% CI: 0.17 to 0.87)], retinopathy [HR = 0.42; (95% CI: 0.21 to 0.86)], and autonomic neuropathy [HR = 0.37; (95% CI: 0.18 to 0.79)].

16. Aspirin Therapy in Diabetes for Prevention of CVD

16A The GDT recommends that patients with diabetes ≥ 40 years old be treated with at least 81 mg/day aspirin unless contraindicated. *Consensus-based*

16B The GDT recommends that people with aspirin allergy, bleeding tendency, age > 85, or clinically active hepatic disease are not candidates for aspirin therapy. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- One RCT[74] was identified which found that low-dose aspirin (100 mg/day) led to a nonsignificant reduction in the main endpoint (CV death, nonfatal MI, and nonfatal stroke), a nonsignificant reduction in total cardiovascular events, and a nonsignificant increase in cardiovascular deaths. This study was underpowered due to its premature stop, so the efficacy of aspirin in the primary prevention of CVD in patients with diabetes cannot be ruled out.
- One systematic review[75] found that, compared with controls, antiplatelet treatment in patients with diabetes and cardiovascular disease did not significantly reduce the combined risk of non-fatal myocardial infarction, non-fatal stroke, death from a vascular cause, or death from an unknown cause (nine RCTs, 4,961 people with diabetes and CVD; 403/2,568 [15.7%] with antiplatelet treatment vs. 426/2,558 [16.7%] with control; RR = 0.94, 95% CI: 0.83 to 1.07). However, antiplatelet therapy significantly reduced the combined outcome of any serious vascular event by 25% in the total high-risk population (n = 135,000). The authors conclude that "given the overall evidence for a reduction in serious vascular events of about one quarter among such a wide range of patients at high-risk of occlusive vascular disease, it would be…inappropriate to base conclusions on the effects of antiplatelet therapy in each small subcategory of patients solely on the results from that subcategory. Although antiplatelet therapy was associated with only a non-significant 7% proportional reduction in serious vascular events among patients with diabetes mellitus (but, predominantly, no history of MI or stroke), these results do not provide reliable evidence of a lack of worthwhile benefit in such patients."
- Although the evidence supports 75 mg aspirin daily, the GDT recommends 81 mg of aspirin because this ASA dose is available in the United States.

Supporting Evidence for Aspirin use in the Primary Prevention of CVD

- One systematic review[33] was found in Clinical Evidence that included three RCTs,[40, 76, 77] and one systematic review[78] that looked at aspirin use in people with diabetes. Two of the RCTs studied primary prevention of cardiovascular outcomes.[40, 59, 76]
- The HOT trial[40] randomized participants with hypertension to either placebo or 75 mg aspirin and followed them for 3.8 years. Of the 18,790 people included in the trial, 1,503 had diabetes. Although the study did not provide the actual results for the diabetes subgroup, the authors did note that aspirin reduced AMI in the diabetes subgroup similar to those patients without diabetes (RR = 0.85).

- The Physicians Health Study[76] included 22,071 healthy males, age 40 to 85, who were randomized to placebo or 325 mg aspirin every other day. 533 of the participants had diabetes. Aspirin was associated with a decrease in fatal or non-fatal MIs within the diabetes subgroup (RR = 0.39; (95% CI: 0.20 to 0.79); NNT = 16; (95% CI: 12 to 47) over five years).
- Aspirin has been shown to prevent MIs in a population with a subgroup of people with diabetes (Physicians Health Study) and in a population that included people with diabetes (HOT) with no prior history of cardiovascular disease.

Supporting Evidence for Aspirin use in the Primary and Secondary Prevention of CVD

- One systematic review[33] was found in Clinical Evidence that included three RCTs,[40, 76, 77] and one systematic review[78] that looked at aspirin use in people with diabetes. One RCT included in the Clinical Evidence systematic review studied the use of aspirin for primary and secondary prevention of CVD.[77]
- ETDRS[77] included 3,711 people with diabetes. 48% of the participants had documented CVD.
- Participants were randomized to 650 mg/day aspirin or placebo and were followed for five years.
- There was a no statistically significant difference in mortality between groups. There were fewer primary and secondary fatal or non-fatal MIs in the treatment group (ARR = 2%; 95% CI: 0.1 to 4.9; NNT = 50).
- Aspirin has been associated with fewer MIs in people with diabetes with and without prior history of cardiovascular disease.

Supporting Evidence for Aspirin use in the Secondary Prevention of CVD

- One systematic review[33] was found in Clinical Evidence that included three RCTs,[40, 76, 77] and one systematic review[78] that looked at aspirin use in people with diabetes. The Antiplatelet Trialists' Collaboration systematic review included 145 RCTs studies and looked at secondary prevention of CVD.[78]
- The studies gave various doses of aspirin ranging from 75 to 1,500 mg aspirin/day. The median follow-up was two years.
- CVD morbidity and mortality were significantly less in the groups that received aspirin (19%) than the control groups (22%). The NNT calculated by Clinical Evidence for the diabetes subgroup was 26 (95% CI: 17 to 66).

Supporting Evidence Regarding the Adverse Effects of Aspirin

- All studies included in the Clinical Evidence systematic review that looked at the effect of aspirin or placebo on CVD reported adverse events.
- No statistically significant differences were found for stroke (fatal and non-fatal) and all GI symptoms (including ulcer) for the various doses of aspirin. These results were for the entire study population, not specifically for the diabetes subgroup.
- The major adverse effects associated with 325 mg aspirin every other day was hemorrhage related to ulcer (RR = 1.78; 95% CI: 1.07 to 2.94; p = 0.04) and bleeding (e.g., easy bruising, hematemesis, melena, non-specific GI, etc.) (RR = 1.32; 95% CI: 1.25 to 1.40; p < 0.00001). These results included both participants with and without diabetes within the Physicians Health Study.

Supporting Evidence for Treatment with Aspirin Based on CVD Risk

- No RCTs were found that looked at the effect of aspirin in people with diabetes at high- or low-risk for CVD.
- One study was found that used a decision analysis model for use of aspirin in primary prevention of CVD.[79] The study included men, without a history of cardiovascular events, with varying risk of developing CVD. The investigators found that aspirin appeared to harm men at low-risk for CVD, while men at high-risk appeared to benefit from aspirin therapy.

Although not formally documented, an analyst at Group Health Cooperative of Puget Sound performed a cost/benefit analysis of risk of GI bleed due to aspirin in patients with diabetes. The costs of complications, related to the adverse effects of GI bleed, exceeded the benefit for a patient with a five-year CAD risk of 4%.

17. Beta-Blocker Therapy for Secondary Prevention of CVD

17 For CAD patients, non-intrinsic sympathomimetic activity (non-ISA) beta-blocker therapy is recommended, unless contraindicated. *Consensus-Based*

*Note: Drugs **without** ISA are atenolol, betaxolol, bisoprolol, carvedilol, labetolol, nadolol, metoprolol, propranolol, and timolol. Drugs **with** ISA are acebutolol, and pindolol.*

Rationale:

Evidence for Recommendation 17: Consensus-based

2009 Update:

These recommendations are excerpted from the 2008 KP National Coronary Artery Disease Clinical Practice Guidelines. KP National is working towards complete alignment and integration of recommendations among the Diabetes, CAD, Hypertension and Dyslipidemia Guidelines, under the oversight of the Integrated Cardiovascular Health Leads (John Merenich, MD, Marc Jaffe, MD, Jim Dudl MD, John Golden MD, Joel Handler MD, and Wiley Chan MD). The first step in this process is to align the mostly minor discrepancies between the existing recommendations that address the same topic. The Diabetes Guideline had several recommendations that had been updated by the other GDTs, and the ICVH Leads felt that it would be best to formally adopt those updated recommendations in the Diabetes Guideline.

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- There is strong evidence that beta-blockers should be given to all patients with a history of MI. See National CAD guidelines (http://cl.kp.org/pkc/national/cmi/programs/cad/management.html).
- Although no RCTs were found that looked at beta-blockers exclusively in patients with diabetes for the secondary prevention of CVD, there are three studies that included patients with diabetes that have documented the benefit of beta-blockade.
- Three studies with non-ideal design, or that did not include a diabetes subgroup analysis, helped inform the recommendation for the use of beta-blockers in secondary prevention of CVD.
- A subgroup analysis within the Bezafibrate Infarction Prevention study[80] was found that included a subgroup of 2,723 non-insulin-dependent people with diabetes. The follow-up was three years.

- The focus was secondary prevention of cardiovascular events, although patients were not randomized to beta-blockers (33% were on beta-blockers, either propranolol or a cardioselective beta-blocker).
- The investigators found a 44% risk reduction ($p < 0.05$) in total mortality and a 42% risk reduction ($p < 0.05$) in cardiac mortality associated with beta-blockers.
- The DIGAMI study[81] also had a subgroup analysis of people with diabetes on beta-blockers.
- DIGAMI randomized 620 people with diabetes who were hospitalized for AMI to either control or an insulin-glucose infusion. Patients were followed for a mean 3.6 years.
- Patients were not randomized to beta-blockers, but a subgroup analysis showed that patients on beta-blockers had a > 50% mortality reduction.
- Beta-blockers appeared to have an independent secondary preventive effect on cardiovascular events.
- A retrospective cohort analysis was found that looked at secondary prevention of CVD in older people with diabetes.[82]
- The study included 45,308 medical records of Medicare patients admitted with AMI in 1994 and 1995 within the National Cooperative Cardiovascular Project.
- After adjusting for confounding factors, beta-blockers were associated with a decrease in one-year mortality for insulin treated patients (hazard ratio = 0.87; 95% CI: 0.72 to 1.07) and non-insulin treated patients (hazard ratio = -0.77; 95% CI: 0.67 to 0.88).
- The evidence suggests that beta-blockers are associated with a decrease in mortality in secondary prevention of CVD both in people with diabetes[81] and in populations that included people with diabetes.[80]

18. Multifactorial Interventions for Prevention of CVD

18 The GDT recommends concurrent treatment of cardiovascular (CV) risk factors for the prevention of CV events in patients with type 2 diabetes. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- The GDT has made recommendations for the individual treatment of CV risk factors based on strong evidence regarding drug therapy (e.g., ACE inhibitors, statins, aspirin, and beta-blockers) for the primary and secondary prevention of CV events.
- Given the strength of these individual recommendations, the fact that CV disease is the leading cause of mortality for patients with diabetes, and that we found no negative studies regarding concurrent treatment of CV risk factors, the GDT believes that it is important to recommend concurrent treatment of CV risk factors for the prevention of CV events in patients with type 2 diabetes.
- In support of this, we also found the STENO-2 RCT[83] which demonstrated that a long-term (eight years) intensified intervention aimed at simultaneous treatment of hyperglycemia, hypertension, dyslipidemia, and microalbuminuria significantly reduced the risk of cardiovascular and microvascular events in patients with type 2 diabetes and micro-albuminuria. Among multiple components in the treatment regimen was treatment with ACE inhibitor (50 mg captopril bid), aspirin (150 mg daily), and statins (atorvastatin, maximum 80 mg daily).

- 160 patients with type 2 diabetes and microalbuminuria were randomized to either conventional treatment or to intensive treatment (stepwise implementation of behavior modification and pharmacological therapy that targeted hyperglycemia, hypertension, dyslipidemia, microalbuminuria, and secondary prevention of CV disease with aspirin).
- Intensive therapy significantly lowered the risk of CV disease [HR = 0.46; (95% CI: 0.24 to 0.73)], nephropathy [HR = 0.39; (95% CI: 0.17 to 0.87)], retinopathy [HR = 0.42; (95% CI: 0.21 to 0.86)], and autonomic neuropathy [HR = 0.37; (95% CI: 0.18 to 0.79)].
- Concerns with this study are:
  - The small size of this study (n = 160).
  - The only CV endpoint reported was a composite endpoint.
  - There were multiple components in this intervention (e.g., low-fat diet, exercise program, strict treatment goals, vitamin supplements, etc.). Thus it cannot be said with certainty whether any individual component or any subsection of the intervention led to the decreased risk of CV disease.
- The presence of multiple components in the STENO-2 intensive intervention (e.g., vitamin supplements, low-fat diet, exercise, etc.) group prohibits an evidence-based recommendation on any particular subset of this intervention without also including the other components in the recommendation. However, a consensus-based recommendation can be made for the concurrent treatment of CV risk factors based on the positive results of the STENO-2 trial and the following:
  - Results from several RCTs suggest that vitamin E and vitamin C do not improve survival or reduce CV events in patients with diabetes.[2, 32]
  - Blood glucose control has not been shown to improve CV outcomes in patients with diabetes.[84-86]
  - There is strong evidence that the singular treatment of hypertension, dyslipidemia, and microalbuminuria with aspirin, ACE inhibitors, and statins decreases macrovascular complications in patients with diabetes.[32, 38, 83]

19. Glucose Control

19 The GDT strongly recommends intensive glucose control in patients with diabetes age < 65 and without serious comorbidities such as CAD, CHF, ESRD, blindness, amputation, stroke or dementia. *Evidence-based: A*

Rationale:

Evidence for Recommendation 19: Good

2007 Update:

New evidence was found that did not change the existing recommendations.

- One meta-analysis (Stettler et al., 2006[87]) was found that suggests that improved glycemic control is associated with a decreased risk of macrovascular disease in patients with diabetes. A greater effect was noted for patients with type 1 diabetes. The reduction in the risk of peripheral vascular disease and stroke in type 2 patients was more significant than the reduction in the risk of cardiac events.

2005 Update:

- One meta-analysis was found which suggests that chronic hyperglycemia is associated with an increased risk of cardiovascular disease in patients with diabetes.[88] This study pooled three studies for type 1 diabetes (n = 1,688) and ten studies for type 2 diabetes (n = 7,435). The pooled relative risk for cardiovascular disease was 1.18 (95% CI: 1.10 to 1.26) and 1.15 (95% CI: 0.92 to 1.43) for each one percentage point increase in glycosylated hemoglobin, for type 2 and type 1 respectively. However, these effects and risk estimates are based on a small number of studies.
- Three systematic reviews within Clinical Evidence were found that looked at the effect of glycemic control on cardiovascular outcomes.
- Herman's systematic review[89] in Clinical Evidence looked at the effect of intensive glucose control on cardiovascular outcomes, microvascular, and neuropathic outcomes, and adverse effects of intensive glucose control. One meta-analysis,[90] and two subsequent RCTs[85, 91] within Herman's systematic review studied the effect of intensive glucose control on CV outcomes. The meta-analysis and one of the RCTs also looked at the microvascular outcomes.
- The Lawson meta-analysis[90] included six RCTs that compared intensive insulin therapy to placebo in people with type 1 diabetes (n = 1,731 for all study populations combined). The studies ranged from two to eight years. No significant impact on macrovascular mortality was found for intensive glucose control (OR = 0.91; 95% CI: 0.31 to 2.65).
- UKPDS 33[85] included 951 newly diagnosed patients with type 2 diabetes (mean age 54, age 48 to 60) who were randomized to either conventional therapy (diet) or intensive therapy (insulin or sulphonylurea). After ten years, intensive therapy did not statistically reduce MI (RRR = 13; 95% CI: –2 to 27) or the combined endpoint of amputation or death from peripheral vascular disease (RRR = 33; 95% CI: –20 to 63).
- Ohkubo[91] compared conventional insulin therapy to intensive insulin therapy in people with type 2 diabetes > 70 years old (mean age 49). 110 participants were followed for six years. No statistically significant differences were seen for CVD, but the study was small and not powered to give significant results for CV events.
- Sigal's systematic review in Clinical Evidence[33] looked at primary and secondary prevention of CVD in people with diabetes. Three RCTs [35, 84-86] were included in Sigal's systematic review that studied intensive glucose control in primary prevention of CVD.
- UKPDS 33[85] is described above (included in the Clinical Evidence systematic review by Herman).
- UKPDS 34[86] randomized 1,704 newly diagnosed people with type 2 diabetes to conventional control (diet), intensive control with metformin, or intensive control with insulin or sulphonylurea. When compared with conventional therapy, metformin was associated with a 32% risk reduction (95% CI: 13 to 47; p = 0.002) of diabetes-related end points (sudden death, hyperglycemia, hypoglycemia, fatal/non-fatal MI, angina, heart failure (HF), stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in one eye, or cataract extraction). Metformin was also linked with fewer MIs (NNT = 16; 95% CI: 10 to 71) in type 2 diabetes. There was a risk reduction in diabetes related deaths associated with metformin of 0.58; (95% CI: 0.37 to 0.91; NNT = 19).
- The DCCT[35, 84] randomized 1,441 people with type 1 diabetes, age 13 to 39, to intensive therapy (external insulin pump or three or more injections per day) or conventional therapy (one to two insulin injections per day). Participants were followed for 6.5 years. There was a decrease in CV events in the intensive therapy group, but the results were not statistically significant.

- Sigal's systematic review[33] in Clinical Evidence looked at primary and secondary prevention of CVD in people with diabetes. Two RCTs were included in Sigal's systematic review that studied intensive glucose control in secondary prevention of CVD, but only one fit our inclusion criteria.[92]
- Abraira[92] randomized men 40 to 69 year old with pre-existing type 2 diabetes to intensive (step therapy insulin injections) vs. conventional glucose lowering therapy (once daily insulin injections). This was a small study (n = 151) with a relatively short follow-up period (27 months). There was no difference in cardiovascular mortality and the difference in new CV events was not statistically different.

Supporting Evidence of the Effect on Microvascular and Neuropathic Outcomes:

- Herman's systematic review[89] in Clinical Evidence looked at the effect of intensive glucose control on cardiovascular outcomes, microvascular, and neuropathic outcomes, and adverse effects of intensive glucose control. Two meta-analyses [90, 93] and three subsequent RCTs[84, 85, 91] were included in Herman's systematic review that looked at the effect of intensive glucose control on microvascular and neuropathic outcomes.
- Wang[93] found 16 small RCTs that included people with type 1 diabetes. Follow-up ranged from eight to 60 months. Intensive glucose control was associated with a decrease in progression of retinopathy (OR = 0.49; 95% CI: 0.28 to 0.85) and development or progression of nephropathy (OR = 0.34; 95% CI: 0.20 to 0.58).
- The Lawson meta-analysis,[90] described in the cardiovascular section, found a positive decrease in microvascular events associated with intensive therapy (OR = 0.55; 95% CI: 0.35 to 0.88).
- UKPDS 33[85] included 951 newly diagnosed patients with type 2 diabetes (mean age 54, age range 48 to 60). Participants were randomized to conventional therapy (diet) or intensive therapy (insulin or sulphonylurea) and followed for ten years. Intensive therapy was associated with a decrease in progression of retinopathy (NNT = 10), and development of neuropathy (NNT = 5).
- The DCCT[84] randomized 1,441 people with type 1 diabetes, age 13 to 39, to intensive therapy (external insulin pump or three or more injections per day) or conventional therapy (one to two insulin injections per day). Participants were followed for 6.5 years. Intensive control was associated with a decrease in development of retinopathy (NNT = 6), progression of retinopathy (NNT = 5), progression or development of nephropathy (NNT = 7), and development or progression of neuropathy (NNT = 13).
- Ohkubo[91] compared conventional insulin therapy to intensive insulin therapy in people with type 2 diabetes. Participants were followed for six years (n = 110). Intensive therapy was associated with a decrease in progression of retinopathy (NNT = 4) and a decrease in progression or development of nephropathy (NNT = 5).
- Intensive glucose control appears to reduce the development and progression of microvascular and neuropathic complications.

Supporting Evidence of the Adverse Effects of Intensive Glucose Control

- Herman's systematic review[89] in Clinical Evidence looked at the effect of intensive glucose control on cardiovascular outcomes, microvascular, and neuropathic outcomes, and adverse effects of intensive glucose control. Twelve RCTs that studied the effect of intensive glucose control on hypoglycemia, weight gain, and quality of life were included in Herman's systematic review.
- The incidence of severe hypoglycemia was higher amongst people with type 1 diabetes in the intensive therapy group (OR = 3.0; 95% CI: 2.5 to 3.6). Rates of major hypoglycemia were significantly greater in the intensive therapy group for patients on insulin, chlopropamide, or glibenclamide ($p < 0.001$).
- BMI significantly increased (by 5.8%) for patients with type 1 diabetes ($p < 0.01$) in the intensive treatment groups. Of the intensive therapies in people with type 2 diabetes, metformin was associated with weight loss while sulphonylurea was associated with weight gain.
- Quality of life was not impacted in the groups with hypoglycemia and weight gain.
- In people with type 2 diabetes, there was a relative risk increase of -12% (95% CI: -17 to 51) for stroke with intensive therapy.
- The adverse effects associated with intensive glucose control should be taken into account when considering intensive therapy.

Overall Conclusion

There is good evidence to recommend intensive glucose control for patients with diabetes, if not contraindicated. While intensive glucose control may result in the adverse effects of hypoglycemia and weight gain,[89] there is good evidence that the positive outcomes of intensive glucose control (e.g., decreased risk of cardiovascular disease, decrease in progression of retinopathy and development or progression of nephropathy, and positive decrease in microvascular events associated with intensive therapy)[88] outweigh its negative effects.

Other Considerations

- Diabetic complications increase when HbA1c concentrations are above the non-diabetic range. There is evidence to support intensive glucose control in both type 1 and 2 diabetes for the prevention of retinopathy, nephropathy, and neuropathy. Intensive treatment is associated with a trend towards improvement in cardiovascular events and there is no evidence that intensive treatment increases incidence of cardiovascular outcomes. Intensive treatment is associated with hypoglycemia and weight gain without adverse impact on quality of life.
- Older adults, people with a history of severe hypoglycemia, or people who are unaware of hypoglycemia may not be good candidates for intensive treatment of type 1 diabetes. The benefits of intensive treatment are limited by the complications of advanced diabetes (blindness, ESRD, or CVD), major comorbidity, and reduced life expectancy. Risk of intensive treatment is increased by history of severe hypoglycemia or unawareness of hypoglycemia, advanced autonomic neuropathy, or CVD, and impaired ability to detect/treat hypoglycemia.
- Intensive glycemic control is especially important in people with onset of type 1 diabetes prior to age 40 and patients with early signs of progression of microvascular complications. Intensive treatment in type 2 diabetes may be less appropriate in people over 65 years or in those with longstanding diabetes.

Results from the EDIC trial[94] (a follow-up to the DCCT trial) seems to confirm that intensive glucose control has a significant effect on decreasing CVD events in patients with type 1 diabetes. After 6.5 years of the DCCT, HbA1c levels averaged 7% in the intensively treated group and 9% in the conventionally treated group. Even though both groups' HbA1c values have leveled off at about 8% after a rise in blood glucose in the intensively treated group and a drop in blood glucose in those formerly on conventional treatment, in the 1,375 volunteers continuing to participate in the study, the intensively treated patients had less than half the number of CVD events than the conventionally treated group (46 compared with 98 events). Such events included heart attacks, stroke, angina, and coronary artery disease requiring angioplasty or coronary bypass surgery. Thirty-one intensively treated patients (4%) and 52 conventionally treated patients (7%) had at least one CVD event during the 17 years of follow-up.

20. Initial Drug Therapy for Glucose Lowering in Type 2 Diabetes

20A The GDT recommends metformin as the first-line glucose lowering drug in patients with type 2 diabetes with BMI > 27. *Evidence-based: B*

20B The GDT recommends metformin as the first-line glucose lowering drug in patients with type 2 diabetes with BMI ≤ 27. *Consensus-based*

Rationale:

Evidence for Recommendation 20A: Good

2007 Update:

New evidence was found that did not change the existing recommendations.

- A Cochrane Collaboration systematic review (Richter, et al., 2006[95]) identified 16 RCTs of pioglitazone monotherapy. A pooled analysis of the data suggests that rosiglitazone therapy is associated with an increased risk of death from any cause, MI, and stroke.
- A Cochrane Collaboration systematic review (Richter, et al., 2007[96]) identified ten RCTs of rosiglitazone monotherapy. Meta-analysis of available data indicated a significantly increased risk of edema.

2005 Update:

- One RCT was found that compared various types of intensive glucose therapy in people with type 2 diabetes.[86]
- UKPDS 34[86] randomized 1,704 newly diagnosed people with type 2 diabetes to conventional control (diet), intensive control with metformin, or intensive control with insulin or sulphonylurea.
- Metformin showed a greater effect than other intensive therapies for any diabetes-related endpoint ($p = 0.0034$) (sudden death, hyperglycemia, hypoglycemia, fatal/non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in one eye, or cataract extraction), all-cause mortality ($p = 0.021$), and stroke ($p = 0.032$).
- When compared with sulphonylurea alone, early addition metformin to sulphonylurea increased diabetes-related death by 96% (95% CI: 2 to 275; $p = 0.039$).
- Potential cross-over bias:
  - In the intensive treatment group with metformin, when hyperglycemia developed, sulphonylurea (glibenclamide) was added. If hyperglycemia developed again, therapy was changed to insulin.
  - In the non-overweight and overweight sulphonylurea treated patients, if a person randomized to sulphonylurea had symptoms of hyperglycemia, metformin was added. If the person on combination sulphonylurea/metformin developed hyperglycemia, the patient was switched to insulin therapy.

- Drug therapy with metformin for intensive glucose control is associated with a decreased risk of diabetes-related end points (including all cause mortality, stroke and any diabetes-related end point). Metformin is also associated with fewer adverse events (weight gain and hypoglycemia) when compared with insulin and sulphonylurea.
- Of the drug therapy for hyperglycemia in people with type 2 diabetes, metformin is superior to insulin and sulphonylurea.
- Only one RCT was found that compared metformin to other glucose lowering therapy and results of this study were questioned by members of the GDT. A compromise recommendation was agreed to such that metformin be considered as the first-line drug for glucose lowering in type 2 diabetes.

Overall Conclusion

There is good evidence to recommend metformin as the first-line glucose-lowering drug in patients with type 2 diabetes with BMI > 27 and BMI ≤ 27. The UKPDS,[86] a large RCT, found good evidence that Metformin, when compared with other intensive therapies, had a greater effect on any diabetes-related endpoint. (e.g., sudden death, stroke, heart failure, renal failure, hyperglycemia). Based upon the evidence from this study, the GDT recommends Metfomin as the first-line glucose-lowering drug in patients with type 2 diabetes.

Other Considerations

- A cost/benefit analysis based on the information from UKPDS 34 was performed using generic pricing for metformin compared with conventional therapy.[97] The analysis revealed that the use of metformin was cost saving in overweight, middle-aged patients with type 2 diabetes. Although this guideline does not include cost analysis, and this analysis was not done with Kaiser Permanente costs, this information may be helpful in creating regional policy.

21. Step Therapy for Glucose Control

21A Following failure to achieve goals on monotherapy, the GDT recommends more than one medication. *Consensus-based*

21B The GDT has determined that there is insufficient evidence to recommend an optimal medication combination for type 2 diabetes not controlled with a single agent. *Consensus-based*

Rationale:

2007 Update:

New evidence was found that did not change the existing recommendations.

- Yki-Jarvinen et al. (Yki-Jarvinen, 2006[98]) reported the results of an RCT comparing NPH insulin with glargine for adult patients whose type 2 diabetes was inadequately controlled by metformin therapy. Both groups achieved good glycemic control. During the first 12 weeks of the 36-week study, hypoglycemic events were more common in the glargine group, but this difference did not persist.

2005 Update:

- UKPDS 49[99] found that three years after diagnosis, 50% of all patients will require more than one drug for glucose control (HbA1c < 7%) and that by year nine, this increases to 75% of all patients.

Sulfonylureas

From an evidence-based review from the National Institute of Clinical Excellence (NICE Clinical Guidelines for Management of type 2 diabetes). (http://www.nice.org.uk/pdf/NICE_full_blood_glucose.pdf)

- "Insulin secretagogues including sulphonylureas and the rapid-acting insulin secretagogues effectively reduce blood glucose levels in people with diabetes."
- "The different insulin secretagogues appear to have comparable glucose lowering effects."
- "In the UKPDS, insulin secretagogues were among glucose lowering therapies which, when considered together, reduced vascular complications compared to lifestyle interventions alone."
- "Glyburide is associated with higher levels of hypoglycemia in comparison with other insulin secretagogues and high rates of life threatening hypoglycemia in population surveillance studies."

Thiazolidinediones (TZDs)

- One meta-analysis did not demonstrate a difference in mortality or CV events between thiazolidinediones and other antidiabetic agents.[100]
- One meta-analysis[101] concluded that:
- Thiazolidinediones lower hemoglobin HbA1c levels by as much as 1.0% to 1.5%.
- Effects can be seen in as little as four weeks, but full lowering takes six to 12 weeks.
- When used in combination with other diabetic agents, such as sulfonylureas and biguanides, TZDs' hypoglycemic effects appear to be complementary.
- Thiazolidinediones directly improve insulin sensitivity and recovery of pancreatic beta cell function.
- Nevertheless, there is no evidence indicating that TZDs are superior to other antidiabetic agents currently available or that TZDs reduce the long-term complications of type 2 diabetes.
- From an evidence-based review from the National Institute of Clinical Excellence (NICE Clinical Guidelines for Management of type 2 diabetes) (http://www.nice.org.uk/pdf/NICE_full_blood_glucose.pdf).
- Thiazolidinediones (TZD) improve blood glucose control as both monotherapy and combination therapy in combination with metformin or sulfonylureas.
- TZDs can improve serum HDL and triglyceride combinations.
- There are no studies yet reported to confirm whether TZDs reduce microvascular or macrovascular complications or how they will perform in this respect in comparison with metformin or insulin secretagogues.
- TZDs result in weight gain, some of which is due to fluid retention.
- After starting TZDs, there may be a delay of six to ten weeks before the full effect is seen.

Insulins

- From an evidence-based review from the National Institute of Clinical Excellence (http://www.nice.org.uk/pdf/NICE_full_blood_glucose.pdf):
- Insulin therapy lowers blood glucose in people with type 2 diabetes.
- In the UKPDS, insulin was among the glucose lowering therapies, which, considered together, reduced vascular complications compared with lifestyle interventions alone.
- Insulin therapy is associated with an increased risk of hypoglycemia greater than any risk from insulin secretagogues.
- There is no direct evidence to support the use of or choice of any one insulin type or regimen over another.
- For people on insulin therapy, glucose control is improved, and body weight and risk of hypoglycemia are reduced when metformin is used in combination.
- For people on insulin therapy, the evidence that blood glucose control is improved when sulphonylureas are taken concomitantly is not conclusive.
- Short-acting insulin analogues appear to be comparable to regular human insulin.
  A Cochrane review of short-acting insulin analogues vs. regular human insulin suggests only a minor benefit of short-acting insulin analogues in the majority of diabetic patients treated with insulin.[102] A meta-analysis[103] suggests only a minor benefit to HbA1c values in adult patients with type 1 diabetes, but no benefit in the remaining population with type 2 or gestational diabetes from SAI analogue treatment.
- Insulin in combination with oral agents appears to be as effective as insulin monotherapy.
  A Cochrane review of insulin monotherapy vs. combinations of insulin with oral hypoglycemic agents in patients with type 2 diabetes concludes that bedtime Neutral Protamine Hagedorn (NPH) insulin combined with oral hypoglycemic agents provide comparable glycemic control to insulin monotherapy and is associated with less weight gain if metformin is used.[104]
- From NICE guidance on long-acting insulin glargine (http://www.nice.org.uk/pdf/Insulin_Analogues.pdf)

  > "For type 1 patients, insulin glargine appears to be more effective than NPH in reducing Fasting Blood Glucose (FBG) but not in reducing HbA1c and there is some evidence that both insulins are as effective as each other in both FBG and HbA1c control. For type 2 patients for whom oral anti-diabetic agents provide inadequate glycaemic control, there is no evidence that insulin glargine is more effective than NPH in reducing either FBG or HbA1c and some evidence that both insulins are as effective as each other is in both FBG and HbA1c control. Evidence for control of hypoglycaemia is equivocal.
  >
  > In studies where insulin glargine is demonstrated to be superior to NPH in controlling nocturnal hypoglycaemia, this may be only apparent when compared with once-daily NPH and not when compared with twice-daily NPH. Further, this superiority of glargine over NPH in the control of nocturnal hypoglycaemia may relate to one formulation of insulin glargine and not another. There is no conclusive evidence that insulin glargine is superior to NPH in controlling symptomatic hypoglycaemia and severe hypoglycaemia. Insufficient data are available to conclude whether insulin glargine is different from each of the commonly used NPH dosing regimens - once-daily and more-than-once-daily."

Overall Conclusion

The UKPDS 49[99] found evidence that three years after diagnosis, 50% of all patients will require more than one drug for glucose control (HbA1c < 7%) and that by year nine, the percentage requiring more than one drug will increase to 75% of all patients. Although there is no evidence indicating that TZDs or sulfonylureas, when used as monotherapy, are superior to other antidiabetic agents available, there is evidence that when these drugs are taken in combination with other diabetic agents, they are effective glucose-lowering therapies when monotherapy fails.

22. Glycemic Control Target

22A An overall treatment goal of HbA1c < 7% is recommended for adults with known diabetes.* *Consensus-based*

22B An individualized HbA1c goal using shared decision-making is recommended.

- A less stringent treatment goal† is recommended for patients > 65 years of age, or with significant comorbidities.*
- Conversely, goals that are more stringent are an option in individual patients.

2009 Update

New evidence was found, the recommendation was changed.

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. See Appendix B for more information on the search strategy.

* HEDIS 2009 lists the following exclusions (comorbidities) for the HbA1c indicator < 7% goal: ≥ 65 years of age; and/or, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the current and/or prior measurement year, regardless of setting; ischemic vascular disease (IVD) in the current and/or prior measurement year, regardless of setting; and, at least one encounter in the measurement year, regardless of setting, of the following — chronic heart failure (CHF); prior myocardial infarction (MI); chronic renal failure (CRF)/end-stage renal disease (ESRD); dementia; blindness; and/or, amputation.

† HEDIS 2009 offers HbA1c < 8% as a treatment goal for those not eligible for the treatment goal of < 7%. Eligibility is to be based on laboratory data to identify the most recent HbA1c test during the measurement year.

Executive Summary

No studies randomizing adults with diabetes to a specific HbA1c target vs. another specific HbA1c target in order to identify the ideal HbA1c target for effective glucose control were identified. Previous iterations of this guideline highlighted indirect evidence, which concluded that better glycemic control is associated with decreased incidence of complications, but with an increased risk of hypoglycemia. Evidence identified in 2009 from studies with long-term follow-up indirectly links intensive glucose control (e.g., HbA1c ≤ 6.5 %, or FPG < 6.0 mmol/L) to reduced cardiovascular risk, including a 10% reduction in risk for CVD, 11% reduction in risk for CHD, and 16% reduction in risk for nonfatal MI. These studies also validated the potential risks of intensive glucose control, including increased mortality (in one study) and a two-fold increased risk for severe hypoglycemia, especially in those with a history of hypoglycemia, advanced atherosclerosis, and advanced age. Even though there is evidence that intensive glycemic control reduces CVD and microvascular disease outcomes, the glycemic control targets varied considerably between trials. Therefore, there is insufficient evidence to determine an optimal target for glycemic control.

In the absence of sufficient evidence, the GDT elected to adopt the NCQA HEDIS targets for blood glucose and, therefore, recommends an overall treatment goal of HbA1c < 7% for adults with known diabetes, and an individualized HbA1c goal (less stringent or more stringent) based on shared decision-making for patients > 65 years of age, and those with comorbid conditions.*

Rationale

A comprehensive systematic review of the literature identified one high-quality systematic review that meta-analyzed five landmark RCTs to determine the effect of intensive glucose control vs. conventional control on cardiovascular outcomes, cardiovascular disease (CVD) mortality and all-cause mortality in patients with type 2 diabetes. It concluded that intensive glucose control results in a 10% reduction in risk for CVD; 11% reduction in risk for CHD; and a 16% reduction in risk for nonfatal MI. The same studies are cited in the American Diabetes Association's (ADA) analysis to support its recommendation to set an overall treatment goal of HbA1c < 7%.

* HEDIS 2009 lists the following exclusions (comorbidities) for the HbA1c indicator < 7% goal: ≥ 65 years of age; and/or, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the current and/or prior measurement year, regardless of setting; ischemic vascular disease (IVD) in the current and/or prior measurement year, regardless of setting; and, at least one encounter in the measurement year, regardless of setting, of the following—chronic heart failure (CHF); prior myocardial infarction (MI); chronic renal failure (CRF)/end-stage renal disease (ESRD); dementia; blindness; and/or, amputation.

Kelly et al. (2009) [105] (N = 28,000) and Ray et al.[106] (N = 33,040) meta-analyzed RCTs to determine the effect of intensive glucose control vs. conventional control on cardiovascular outcomes, cardiovascular disease (CVD) mortality and all-cause mortality in patients with type 2 diabetes. Ray reviewed the ADVANCE (2008), VADT (2009), UKPDS 33 and 34 (1998) (combined as one), ACCORD (2008), and PROactive (2004) studies. Kelly reviewed the ADVANCE (2008), VADT (2009), UKPDS 33 (1998), UKPDS 34 (1998) and the ACCORD (2008) trials. PROactive, an RCT that examined the impact of piaglitazone on surrogates of atherosclerosis, did not meet Kelly's inclusion criteria, as it did not have a priori specification of glycemic goals for the intensive and conventional glucose control groups, which are outcomes of interest for this KP review's clinical question. Furthermore, PROactive has been criticized elsewhere for its composite primary endpoints, which included physician-driven as opposed to disease-driven outcomes, including events in multiple vascular beds (cerebral, cardiac, and peripheral). As such, this KP review will only report on the results of the Kelly meta-analysis, supplemented by additional information from the Ray review. It is notable that the ACCORD study was prematurely ended due to excess mortality in the intensive control group.

The Kelly meta-analysis was conducted with great methodological rigor. It used relative risk and risk difference measures to identify the effect of glucose control on the outcomes of interest, pooling the results using both fixed-effects and random-effects models, and assessing heterogeneity using the DerSimonian and Laird Q test. The authors decided to present pooled results from the random-effects model when they noted heterogeneity ($P < 0.100$) in median diabetes duration, achieved HbA1c levels, and therapeutic regimens. Regardless of the Kelly meta-analysis' robust approach, its review is inevitably affected by biases present in each of the studies, including but not limited to selection bias and publication bias. In addition, when analyzing the effect of intensive glucose control, the review used summary data from the studies and did not analyze individual participant data. Therefore, patient subgroup analysis is not possible. Even though the authors do not provide a power calculation, the large sample size [N = 27,802] invariably helps reduce the confidence interval for the estimate to an acceptable range (i.e., 95% CI: 0.83 to 0.98).

This meta-analysis concluded that intensive glucose control results in a 10% reduction in risk for CVD; 11% reduction in risk for CHD; and a 16% reduction in risk for nonfatal MI. It did not report risk reduction in cardiovascular and all-cause mortality, or fatal MI. Furthermore, it reported a two-fold increased risk for severe hypoglycemia (absolute increase of 39 events per 1,000 patients over five years). A summary of the effect of intensive glucose control on the most important health outcomes is presented below (for all outcomes, see Table 2, and Figures 2 to 4 below).

The benchmark studies cited in the Kelly meta-analysis looked at the following composite endpoints: cardiovascular disease, coronary heart disease, stroke, congestive heart failure, cardiovascular deaths, peripheral artery disease (amputations from PAD) (not addressed in ACCORD), severe hypoglycemia (See Figure 2 below). All other outcomes and side effects of interest to this KP review were not addressed in detail and therefore a statement regarding their relationship to intensive glucose control cannot be made at this time.

Table 1. **Characteristics of 5 Randomized, Controlled Trials of Intensive Glucose Control**

Characteristic	UKPDS 33, 1998 (8)	UKPDS 34, 1998 (11)	ACCORD, 2008 (12)	ADVANCE, 2008 (13)	VADT, 2009 (14)
Participants, *n*	3867	753	10 251	11 140	1791
Median duration of intervention, *y*	10.0	10.7	3.4	5.0	5.6
Treatment					
Intensive glucose control	Sulfonylurea or insulin	Metformin	≥2 classes of hypoglycemic agents plus other drugs	Gliclazide plus other drugs	Glimepiride or metformin, plus rosiglitazone, or insulin
Conventional glucose control	Diet	Diet	Diet or pharmacologic treatment, or both	Continue current therapy, if necessary; patients taking gliclazide substituted the drug with another sulfonylurea	Glimepiride or metformin, plus rosiglitazone, or insulin
Treatment goal					
Intensive glucose control	FPG level <6.0 mmol/L (<108 mg/dL)	FPG level <6.0 mmol/L (<108 mg/dL)	HbA_{1c} level <6.0%	HbA_{1c} level ≤6.5%	HbA_{1c} level <6% and 1.5% less than conventional
Conventional glucose control	FPG level, 6.1–15.0 mmol/L (110–270 mg/L)	FPG level, 6.1–15.0 mmol/L (110–270 mg/L)	HbA_{1c} level, 7.0%–7.9%	Local standards	HbA_{1c} level <9% and 1.5% higher than intensive
Mean age, *y*	53.3	53.0	62.2	66.0	60.4
Men, %	61	47	61	58	97
Race/ethnicity, %					
White	81	86	64	NR	62
Asian	10	5	NR	NR	NR
Black	8	8	19	NR	17
Hispanic	NR	NR	7	NR	16
Other	1	1	NR	NR	5
Mean duration of diabetes, *y*	0.0*	0.0*	10.0†	7.9	11.5
Aspirin use, %	2	2	55	44	NR
History of cardiovascular disease, %	NR	NR	35	32	40

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; NR = not reported; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

* The UKPDS 33 and 34 trials recruited participants with newly diagnosed diabetes.

† Median.

Table 2. **Risk Factors for Cardiovascular Disease in Trial Participants Before and After the Intervention**

Risk Factor	UKPDS 33, 1998 (8)		UKPDS 34, 1998 (11)		ACCORD, 2008 (12)		ADVANCE, 2008 (13)		VADT, 2009 (14)	
	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control
Mean weight, *kg*										
Before intervention	78.1	77.3	87.0	87.0	93.6	93.5	78.0	78.2	96.3*	96.3*
After intervention	79.0†	80.0†	87.0†	86.0†	94.0‡	97.0‡	77.0	78.1	100.4*	104.4*
Mean body mass index, kg/m^2										
Before intervention	28	28	32	32	32	32	28	28	31	31
After intervention	29	29	32	32	NR	NR	28	28	32	34
Mean blood pressure, *mm Hg*										
Systolic										
Before intervention	135	135	140	140	137	136	145	145	132	131
After intervention	138	139	139	141	127	126	138	136	125	127
Diastolic										
Before intervention	82	83	86	85	75	75	81	81	76	76
After intervention	77	77	77	78	68	67	74	74	69	68
Lipid levels, *mmol/L (mg/dL)*										
Median triglyceride										
Before intervention	2.31 (204§)‖	2.37 (210§)‖	2.96 (262§)‖	2.79 (247§)‖	1.74§ (154)	1.76§ (156)	1.64 (145§)	1.60 (142§)	2.52§ (223)	2.27§ (201)
After intervention	1.45§ (128)	1.45§ (127)	1.62§ (143)	1.77§ (157)	NR	NR	1.59 (141§)	1.45 (128§)	1.80§ (159)	1.71§ (151)
Mean HDL cholesterol										
Before intervention	1.08 (42¶)	1.07 (41¶)	1.04 (40¶)	1.06 (41¶)	1.09¶ (42)	1.09¶ (42)	1.25 (48¶)	1.26 (49¶)	0.93¶ (36)	0.93¶ (36)
After intervention	1.11¶ (43)	1.09¶ (42)	1.04¶ (40)	1.11¶ (42)	NR	NR	1.25 (48¶)	1.24 (48¶)	1.06¶ (41)	1.04¶ (40)
Mean LDL cholesterol										
Before intervention	3.5 (135¶)	3.5 (135¶)	3.66 (141¶)	3.67 (142¶)	2.72¶ (105)	2.72¶ (105)	3.11 (120¶)	3.12 (121¶)	2.80¶ (108)	2.77¶ (107)
After intervention	3.26¶ (126)	3.26¶ (126)	3.34¶ (129)	3.37¶ (130)	2.36¶ (91)	2.36¶ (91)	2.65 (102¶)	2.64 (102¶)	2.07¶ (80)	2.07¶ (80)
Median hemoglobin A_{1c} level, %										
Before intervention	6.9**	7.0**	7.0**	7.0**	8.1	8.1	7.2	7.2	9.4††	9.4††
After intervention	8.5	7.9	8.9	8.4	7.2	6.2	7.0	6.3	8.5	7.1

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

* Estimated on the basis of reported weight in pounds by using a conversion factor of 0.45.

† Median.

‡ Calculated on the basis of net change in weight over the study period.

§ Estimated by multiplying (dividing) by a conversion factor of 0.0113.

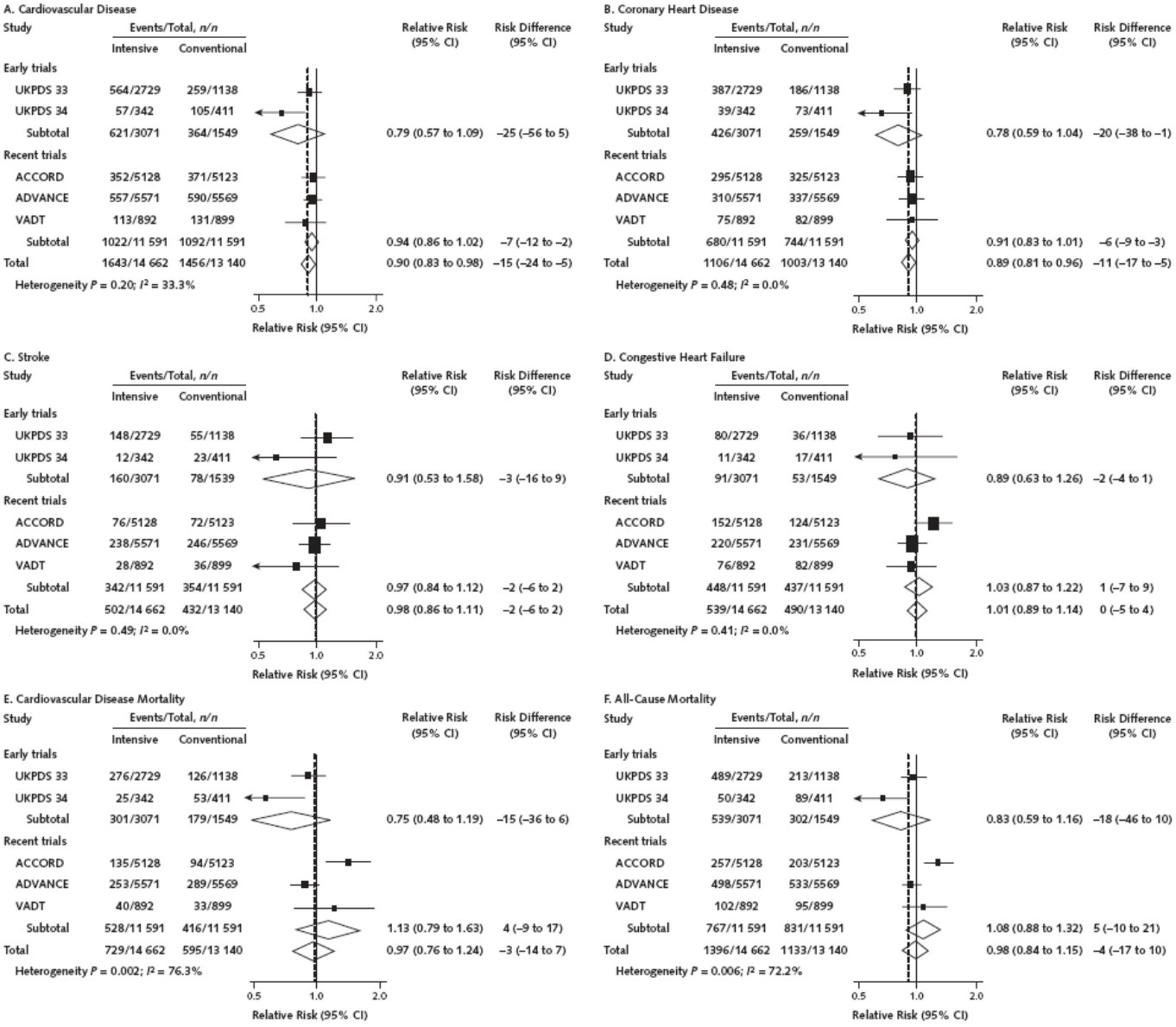
‖ Geometric mean.

¶ Estimated by multiplying (dividing) by a conversion factor of 0.0259.

** Estimated from figure.

†† Mean.

Figure 1. Pooled relative risk and risk difference (per 1,000 patients over five years of treatment) estimates, with 95% CIs, for main study outcomes, by trial, early and more recent trial subgroups, and overall.

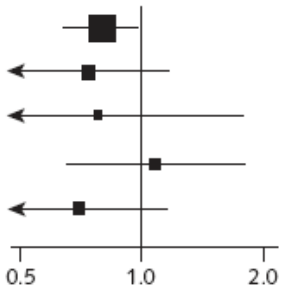


ACCORD = Action to Control Cardiovascular Risk in Diabetes (12); ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (13); UKPDS = United Kingdom Prospective Diabetes Study (8, 11); VADT = Veterans Affairs Diabetes Trial (14).

Figure 2. Pooled relative risk and risk difference (per 1,000 patients over five years of treatment) estimates of nonfatal MI, fatal MI, nonfatal stroke, and PAD.

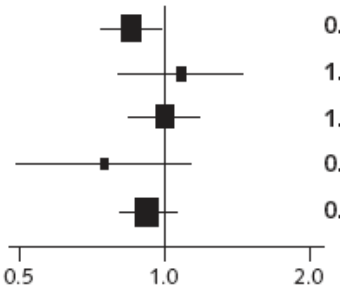
A. Early Trials

Event	Events/Total, *n/n*		Relative Risk (95% CI)	Risk Difference (95% CI)
	Intensive	Conventional		
Nonfatal MI	221/3071	141/1549	0.80 (0.65 to 0.98)	–9 (–13 to –5)
Fatal MI	250/3071	150/1549	0.74 (0.46 to 1.18)	–13 (–29 to 3)
Nonfatal stroke	120/3071	60/1549	0.78 (0.34 to 1.79)	–4 (–15 to 7)
Fatal stroke	49/3071	24/1549	1.08 (0.65 to 1.80)	0 (–3 to 3)
PAD	35/3071	27/1549	0.70 (0.42 to 1.17)	–3 (–4 to –1)



B. Recent Trials

Event	Events/Total, *n/n*		Relative Risk (95% CI)	Risk Difference (95% CI)
	Intensive	Conventional		
Nonfatal MI	390/11 591	457/11 591	0.85 (0.74 to 0.99)	–9 (–20 to 1)
Fatal MI	290/11 591	287/11 591	1.08 (0.80 to 1.46)	3 (–5 to 11)
Nonfatal stroke	303/11 591	302/11 591	1.00 (0.85 to 1.19)	–2 (–7 to 4)
Fatal stroke	39/11 591	52/11 591	0.75 (0.49 to 1.14)	–1 (–3 to 1)
PAD	374/6463	406/6468	0.92 (0.81 to 1.06)	–5 (–9 to –1)



C. All Trials

Event	Events/Total, *n/n*		Relative Risk (95% CI)	Risk Difference (95% CI)
	Intensive	Conventional		
Nonfatal MI	611/14 662	598/13 140	0.84 (0.75 to 0.94)	–9 (–16 to 3)
Fatal MI	540/14 662	437/13 140	0.94 (0.75 to 1.18)	–3 (–10 to 4)
Nonfatal stroke	423/14 662	362/13 140	0.98 (0.82 to 1.17)	–3 (–7 to 2)
Fatal stroke	88/14 662	76/13 140	0.87 (0.63 to 1.20)	0 (–2 to 1)
PAD	409/9534	433/8017	0.91 (0.79 to 1.03)	–3 (–5 to –1)

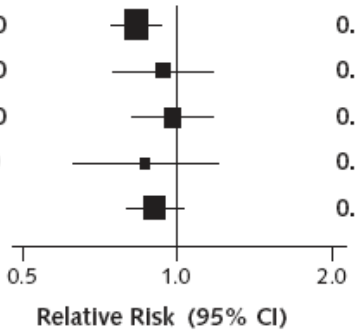
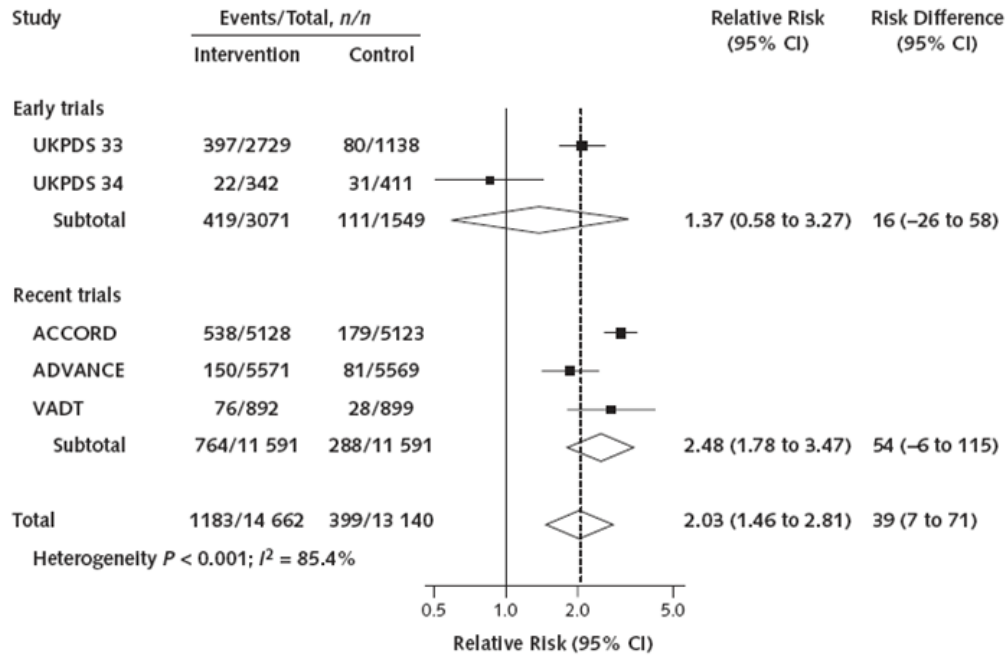


Figure 3. Pooled relative risk and risk difference (per 1,000 patients over five years of treatment) estimates of severe hypoglycemia, by trial, early and more recent trial subgroups, and overall.



ACCORD = Action to Control Cardiovascular Risk in Diabetes (12); ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (13); UKPDS = United Kingdom Prospective Diabetes Study (8, 11); VADT = Veterans Affairs Diabetes Trial (14).

Supplemental Information

American Diabetes Association: Standards of Medical Care in Diabetes—2009[*]

Excerpt begins.

Recommendation: Glycemic Goals in Adults

- Lowering A1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, for microvascular disease prevention, the A1c goal for nonpregnant adults in general is < 7%. (A)
- In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) cohorts suggests that treatment to A1c targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of < 7% appears reasonable for many adults for macrovascular risk reduction. (B)

* For an explanation of the letter grading in this excerpt, please see Appendix C.

- Subgroup analyses of clinical trials such as the DCCT and UKPDS and the microvascular evidence from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial suggest a small but incremental benefit in microvascular outcomes with A1c values closer to normal. Therefore, for selected individual patients, providers might reasonably suggest even lower A1c goals than the general goal of < 7%, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. (B)
- Conversely, less stringent A1c goals than the general goal of < 7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. (C)

Rationale:

Glycemic control is fundamental to the management of diabetes. The DCCT, a prospective, randomized, controlled trial of intensive versus standard glycemic control in patients with relatively recently diagnosed type 1 diabetes, showed definitively that improved glycemic control is associated with significantly decreased rates of microvascular (retinopathy and nephropathy) as well as neuropathic complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown persistence of this effect in previously intensively treated subjects, even though their glycemic control has been equivalent to that of previous standard arm subjects during follow-up.

In type 2 diabetes, the Kumamoto study and the UKPDS demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy. Similar to the DCCT-EDIC findings, long-term follow-up of the UKPDS cohort has recently demonstrated a "legacy effect" of early intensive glycemic control on long-term rates of microvascular complications, even with loss of glycemic separation between the intensive and standard cohorts after the end of the randomized controlled. In each of these large randomized prospective clinical trials, treatment regimens that reduced average A1c to ≥ 7% (≥ 1% above the upper limits of normal) were associated with fewer long-term microvascular complications; however, intensive control was found to increase the risk of severe hypoglycemia, most notably in the DCCT, and led to weight gain. Epidemiological analyses of the DCCT and UKPDS demonstrate a curvilinear relationship between A1c and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair or good control. These analyses also suggest that further lowering of A1c from 7 to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller.

Given the substantially increased risk of hypoglycemia (particularly in those with type 1 diabetes) and the relatively much greater effort required to achieve near normoglycemia, the risks of lower targets may outweigh the potential benefits on microvascular complications on a population level. However, selected individual patients, especially those with little comorbidity and long life expectancy (who may benefit from further lowering of HgbA1c below 7%) may, at patient and provider judgment, adopt glycemic targets as close to normal as possible as long as significant hypoglycemia does not become a barrier. Whereas many epidemiologic studies and meta-analyses have clearly shown a direct relationship between A1c and CVD, the potential of intensive glycemic control to reduce CVD has been less clearly defined. In the DCCT, there was a trend toward lower risk of CVD events with intensive control (risk reduction 41%, 95% CI: 10% to 68%), but the number of events was small. However, nine-year post-DCCT follow-up of the cohort has shown that participants previously randomized to the intensive arm had a 42% reduction (P = 0.02) in CVD outcomes and a 57% reduction (P = 0.02) in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with those previously in the standard arm. The UKPDS trial of type 2 diabetes observed a 16% reduction in cardiovascular complications (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm, although this difference was not statistically significant (P = 0.052), and there was no suggestion of benefit on other CVD outcomes such as stroke. In an epidemiologic analysis of the study cohort, a continuous association was observed, such that for every percentage point lower median on study A1c (e.g., 8 to 7%) there was a statistically significant 18% reduction in CVD events, again with no glycemic threshold.

A recent report of ten years of follow-up of the UKPDS cohort describes, for the participants originally randomized to intensive glycemic control compared with those randomized to conventional glycemic control, long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy, both statistically significant) and in all-cause mortality (13% and 27%, respectively, both statistically significant). Because of ongoing uncertainty regarding whether intensive glycemic control can reduce the increased risk of CVD events in people with type 2 diabetes, several large long-term trials were launched in the past decade to compare the effects of intensive versus standard glycemic control on CVD outcomes in relatively high-risk participants with established type 2 diabetes.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 10,251 participants with either history of a CVD event (ages 40 to 79 years) or significant CVD risk (ages 55 to 79) to a strategy of intensive glycemic control (target A1c < 6.0%) or standard glycemic control (A1c target 7.0 to 7.9%). Investigators used multiple glycemic medications in both arms. ACCORD participants were on average 62 years old and had a mean duration of diabetes of ten years, with 35% already treated with insulin at baseline. From a baseline median A1c of 8.1%, the intensive arm reached a median A1c of 6.4% within 12 months of randomization, while the standard group reached a median A1c of 7.5%. Other risk factors were treated aggressively and equally in both groups. The intensive glycemic control group had more use of insulin in combination with multiple oral agents, significantly more weight gain, and more episodes of severe hypoglycemia than the standard group.

In February 2008, the glycemic control study of ACCORD was halted on the recommendation of the study's data safety monitoring board due to the finding of an increased rate of mortality in the intensive arm compared with the standard arm (1.41%/year vs. 1.14%/year; HR = 1.22 [95% CI: 1.01 to 1.46]), with a similar increase in cardiovascular deaths. The primary outcome of ACCORD (MI, stroke, or cardiovascular death) was lower in the intensive glycemic control group due to a reduction in nonfatal MI, although this finding was not statistically significant when the study was terminated (HR = 0.90 [95% CI: 0.78 to 1.04]; P = 0.16).

Exploratory analyses of the mortality findings of ACCORD (evaluating variables including weight gain, use of any specific drug or drug combination, and hypoglycemia) were reportedly unable to identify an explanation for the excess mortality in the intensive arm. Pre-specified subset analyses showed that participants with no previous CVD event and those who had a baseline A1c < 8% had a statistically significant reduction in the primary CVD outcome.

The ADVANCE study randomized 11,140 participants to a strategy of intensive glycemic control (with primary therapy being the sulfonylurea gliclizide and additional medications as needed to achieve a target A1c of < 6.5%) or to standard therapy (in which any medication but gliclizide could be used and the glycemic target was according to "local guidelines"). ADVANCE participants (who had to be at least 55 years of age with either known vascular disease or at least one other vascular risk factor) were slightly older and of similar high CVD risk as those in ACCORD. However, they had an average duration of diabetes two years shorter, lower baseline A1c (median 7.2%), and almost no use of insulin at enrollment. The median A1c levels achieved in the intensive and standard arms were 6.3 and 7.0%, respectively, and maximal separation between the arms took several years to achieve. Use of other drugs that favorably impact CVD risk (aspirin, statins, ACE inhibitors) was lower in ADVANCE than in the ACCORD or Veterans Affairs Diabetes Trial (VADT).

The primary outcome of ADVANCE was a combination of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death). Intensive glycemic control significantly reduced the primary endpoint (HR = 0.90 [95% CI: 0.82 to 0.98]; P = 0.01), although this was due to a significant reduction in the microvascular outcome (0.86 [95% CI: 0.77 to 0.97], P = 0.01), primarily development of macroalbuminuria, with no significant reduction in the macrovascular outcome (0.94 [95% CI: 0.84 to 1.06]; P = 0.32). There was no difference in overall or cardiovascular mortality between the intensive and the standard glycemic control arms.

The VADT randomized 1,791 participants with type 2 diabetes uncontrolled on insulin or maximal dose oral agents (median entry A1c = 9.4%) to a strategy of intensive glycemic control (goal A1c < 6.0%) or standard glycemic control, with a planned A1c separation of at least 1.5%. Medication treatment algorithms were used to achieve the specified glycemic goals, with a goal of using similar medications in both groups. Median A1c levels of 6.9 and 8.4% were achieved in the intensive and standard arms, respectively, within the first year of the study. Other CVD risk factors were treated aggressively and equally in both groups. The primary outcome of the VADT was a composite of CVD events (MI, stroke, cardiovascular death, revascularization, hospitalization for heart failure, and amputation for ischemia).

During a mean six-year follow-up period, the cumulative primary outcome was nonsignificantly lower in the intensive arm (HR = 0.87 [95% CI: 0.73 to 1.04]; P = 0.12). There were more CVD deaths in the intensive arm than in the standard arm (40 vs. 33; sudden deaths 11 vs. 4), but the difference was not statistically significant. Post hoc subgroup analyses suggested that duration of diabetes interacted with randomization such that participants with duration of diabetes less than about 12 years appeared to have a CVD benefit of intensive glycemic control while those with longer duration of disease before study entry had a neutral or even adverse effect of intensive glycemic control. Other exploratory analyses suggested that severe hypoglycemia within the past 90 days was a strong predictor of the primary outcome and of CVD mortality.

The cause of the excess deaths in the intensive glycemic control arm of ACCORD compared with the standard arm has been difficult to pinpoint. By design of the trial, randomization to the intensive arm was associated with or led to many downstream effects, such as higher rates of severe hypoglycemia; more frequent use of insulin, TZDs, other drugs, and drug combinations; and greater weight gain. Such factors may be associated statistically with the higher mortality rate in the intensive arm but may not be causative.

It is biologically plausible that severe hypoglycemia could increase the risk of cardiovascular death in participants with high underlying CVD risk. Other plausible mechanisms for the increase in mortality in ACCORD include weight gain, unmeasured drug effects or interactions, or the overall "intensity" of the ACCORD intervention (use of multiple oral glucose-lowering drugs along with multiple doses of insulin, frequent therapy adjustments to push A1c and self-monitored blood glucose to very low targets, and an intense effort to aggressively reduce A1c by ~2% in participants entering the trial with advanced diabetes and multiple comorbidities).

Since the ADVANCE trial did not show any increase in mortality in the intensive glycemic control arm, examining the differences between ADVANCE and ACCORD supports additional hypotheses. ADVANCE participants on average appeared to have earlier or less advanced diabetes, with shorter duration by two to three years and lower A1c at entry despite very little use of insulin at baseline. A1c was also lowered less and more gradually in the ADVANCE trial, and there was no significant weight gain with intensive glycemic therapy. Although severe hypoglycemia was defined somewhat differently in the three trials, it appears that this occurred in fewer than 3% of intensively treated ADVANCE participants for the entire study duration (median five years) compared with ~16% of intensively treated subjects in ACCORD and 21% in VADT.

It is likely that the increase in mortality in ACCORD was related to the overall treatment strategies for intensifying glycemic control in the study population, not the achieved A1c per se. The ADVANCE study achieved a median A1c in its intensive arm similar to that in the ACCORD study, with no increased mortality hazard. Thus, the ACCORD mortality findings do not imply that patients with type 2 diabetes who can easily achieve or maintain low A1c levels with lifestyle modifications with or without pharmacotherapy are at risk and need to "raise" their A1c. The three trials compared treatments to A1c levels in the "flatter" part of the observational glycemia-CVD risk curves (median A1c of 6.4 to 6.9% in the intensive arms compared with 7.0 to 8.4% in the standard arms). Importantly, their results should not be extrapolated to imply that there would be no cardiovascular benefit of glucose lowering from very poor control (e.g., A1c > 9%) to good control (e.g., A1c < 7%).

All three trials were carried out in participants with established diabetes (mean duration eight to eleven years) and either known CVD or multiple risk factors suggesting the presence of established atherosclerosis. Subset analyses of the three trials suggested a significant benefit of intensive glycemic control on CVD in participants with shorter duration of diabetes, lower A1c at entry, and/or or absence of known CVD. The DCCT-EDIC study and the long-term follow-up of the UKPDS cohort both suggest that intensive glycemic control initiated soon after diagnosis of diabetes in patients with a lower level of CVD risk may impart long-term protection from CVD events. As is the case with microvascular complications, it may be that glycemic control plays a greater role before macrovascular disease is well developed and minimal or no role when it is advanced.

The benefits of intensive glycemic control on microvascular and neuropathic complications are well established for both type 1 and type 2 diabetes. The ADVANCE trial has added to that evidence base by demonstrating a significant reduction in the risk of new or worsening albuminuria when A1c was lowered to 6.3% compared with standard glycemic control achieving an A1c of 7.0%. The lack of significant reduction in CVD events with intensive glycemic control in ACCORD, ADVANCE, and VADT should not lead clinicians to abandon the general target of an A1c < 7.0% and thereby discount the benefit of good control on what are serious and debilitating microvascular complications.

The evidence for a cardiovascular benefit of intensive glycemic control primarily rests on long-term follow-up of study cohorts treated early in the course of type 1 and type 2 diabetes and subset analyses of ACCORD, ADVANCE, and VADT. Conversely, the mortality findings in ACCORD suggest that the potential risks of very intensive glycemic control may outweigh its benefits in some patients, such as those with very long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age/frailty. Certainly, providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1c levels in patients in whom such a target cannot be reasonably easily and safely achieved.

Recommended glycemic goals for nonpregnant adults are shown in Table 9. The recommendations are based on those for A1c, with listed blood glucose levels that appear to correlate with achievement of an A1c of < 7%. The issue of pre- versus postprandial SMBG targets is complex. Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of FPG in some epidemiological studies. In diabetic subjects, some surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1c levels, with its relative contribution being higher at A1c levels that are closer to 7%. However, outcome studies have clearly shown A1c to be the primary predictor of complications, and landmark glycemic control trials such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG.

Additionally, a randomized, controlled trial presented at the 68th Scientific Sessions of the American Diabetes Association in June 2008 found no CVD benefit of insulin regimens targeting postprandial glucose compared with those targeting preprandial glucose. A reasonable recommendation for postprandial testing and targets is that for individuals who have premeal glucose values within target but have A1c values above target, monitoring postprandial plasma glucose (PPG) 1 to 2 hours after the start of the meal and treatment aimed at reducing PPG values to < 180 mg/dl may help lower A1c.

As noted above, less stringent treatment goals may be appropriate for adults with limited life expectancies or advanced vascular disease. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals.

Regarding goals for glycemic control for women with GDM, recommendations from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus were to target the following maternal capillary glucose concentrations:

- preprandial ≤ 95 mg/dl (5.3 mmol/l) and either
- 1-h postmeal: ≤ 140 mg/dl (7.8 mmol/l)

  or
- 2-h postmeal: ≤ 120 mg/dl (6.7 mmol/l)

For women with preexisting type 1 or type 2 diabetes who become pregnant, a recent consensus statement recommended the following as optimal glycemic goals, if they can be achieved without excessive hypoglycemia:

- premeal, bedtime, and overnight glucose 60 to 99 mg/dl
- peak postprandial glucose 100 to 129 mg/dl
- A1c < 6.0%

End of Excerpt.

2007 Guideline

No new evidence was found, the recommendation remains unchanged.

2005 Guideline

- No studies were found that randomized people with diabetes to blood glucose targets that were normal (e.g., HbA1c < 6%) or above normal (HbA1c > 6%).
- One systematic review[89] was found in Clinical Evidence that included two RCTs[84, 85] that randomized people with diabetes to either intensive or conventional glucose control and reported the effect of HbA1c on health outcomes (all risk reductions were calculated by Clinical Evidence).
- Each 1% decrease in HbA1c was associated with a reduced risk in microvascular and macrovascular events (RR = 0.79; 95% CI: 0.79 to 0.83).
- For each 1% decrease in HbA1c, the risk reduction of diabetes related death was 0.79 (95% CI: 0.73 to 0.83) and 0.86 (95% CI: 0.81 to 0.91) for all causes of mortality.
- Microvascular complications decreased with each 1% decrease in HbA1c (RR = 0.63; 95% CI: 0.59 to 0.67).
- The risk reduction for MI was 0.86 (95% CI: 0.79 to 0.92) for each 1% decrease in HbA1c.
- Hypoglycemia was associated with intensive treatment in both RCTs.
- As concentrations of HbA1c were reduced, the risk of complications decreased but the risk of hypoglycemia increased. The risk of complications associated with uncontrolled diabetes decreased and the risk of hypoglycemia increased with lower glycemic thresholds.
- The results of these studies suggest that there is no lower glycemic threshold for the risk of complications. The better the glycemic control, the lower the risk of complications.

Overall Conclusion

Based upon good evidence showing that better glycemic control is associated with decreased incidence of complications, but insufficient evidence about a specific threshold, the GDT has made a consensus recommendation that the overall treatment goal for HbA1c < 7.

Other Considerations

- The ADA recommends that providers develop or adjust the management plan to achieve normal or near-normal glycemia with an HbA1c goal of < 7%. The guidelines also include the following statements/recommendations:
- Lowering HbA1c has been associated with a reduction of microvascular and neuropathic complications of diabetes.
- More stringent goals (i.e., a normal HbA1c, < 6%) can be considered in individual patients and in pregnancy.
- A lower HbA1c is associated with a lower risk of myocardial infarction and cardiovascular death.
- Aggressive glycemic management with insulin may reduce morbidity in patients with severe acute illness, perioperatively, following myocardial infarction and in pregnancy.
- Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children, or older adults, and individuals with comorbid conditions.
- The American College of Endocrinology recommends targets for glycemic control of HbA1c < 6.5%.[107]
- Others have attempted to quantify HbA1c targets based upon age of onset of diabetes and have tried to develop criteria starting with lower HbA1c's at age < 45 compared with higher HbA1c's at age > 75.

- It may be appropriate to target a less intensive goal for people who may have limited benefit or increased risk with intensive treatment. It is best if HbA1c reflects a person's self determined goals of care and willingness to make lifestyle modifications.
- In the opinion of the GDT, no studies have shown that there is one specific HbA1c target that balances the risks and benefits of achieving that target.

23. Microalbumin Assessments for Patients with Diabetes and Documented Microalbuminuria on ACE Inhibitors or ARBs

23 The GDT recommends that continued monitoring of microalbumin be optional in people with diabetes and established microalbuminuria, who are on an ACE inhibitor or ARB. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- There is preliminary evidence that repeated testing of microalbumin levels might be justified in order to measure the effectiveness of treatment, although this practice is not mandatory.
- One RCT was found that included 199 patients with type 2 diabetes with hypertension and microalbuminuria.(51) The investigator found that patients showed improvement in mean urinary albumin:creatinine outcomes when an ARB was added to the regimen.
- One short-term RCT looked at intermediate outcomes and reported that ≥ 60 mg ACE inhibitor showed progressive improvement in glomerular filtration rate (GFR), significant change in albuminuria, and kidney size.(108)

Other Considerations

- Experts are often asked if patients with microalbuminuria and diabetes who are on an ACE inhibitor should have their microalbumin levels monitored.
- HEDIS requires that a test for microalbumin be done every year for people with diabetes unless the person has documented evidence of nephropathy (e.g., ESRD, renal failure, diabetic nephropathy, dialysis, positive microalbumin test in prior year) or who had a negative microalbumin test in the prior year and are either not on insulin or their HbA1c is < 8%.(109)
- The ADA states the following regarding testing for microalbuminuria after diagnosis: "The role of annual urine protein dipstick testing and microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of ACE inhibitor therapy and blood pressure control. Many experts recommend continued surveillance both to assess response to therapy and progression of disease. In addition to assessment of urinary albumin excretion, assessment of renal function is important in patients with diabetic kidney disease."(21)

24. Retinal Screening

24 The GDT recommends that diabetes patients with background retinopathy, or more severe disease, should be monitored at least annually; and those without retinopathy should be screened every one to two years. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

Supporting Evidence that Treating Retinopathy can Prevent Blindness

- There is evidence that retinal laser therapy is highly effective in slowing the progression of retinopathy and preventing blindness (laser surgery recommendation not included in the scope of these guidelines).[110, 111]
- The leading cause of blindness in people with diabetes is vitreous or preretinal hemorrhage, followed by macular edema or macular pigmentary changes related to macular edema, and retinal detachment. An eye exam can detect retinopathy before it progresses beyond the point of repair. Clinically significant macular edema (CSME) has been found to be associated with benefit from focal or grid laser treatment. Treatments at earlier stages of macular edema were not associated with benefit.
- There is no evidence that screening every one to two years prevents blindness.

Supporting Evidence that Retinopathy Leads to Macular Edema or Proliferative Retinopathy

- There are no good studies to recommend screening or a frequency of screening.
- Three observational cohort studies were found that show diabetic retinopathy leads to macular edema or proliferative retinopathy.[112] The publications are subanalyses of a single diabetes cohort where patients with diabetes were followed for four years. Each patient received a physical and ocular exam (slit lamp, stereoscopic fundus photo with seven standard fields). Experts graded each photo. Because of the subjective nature of grading, the experts did not always agree on the grade.

Diabetic Retinopathy (Without Macular Edema) in People With Diabetes Age < 30

- The first study included 996 young (age < 30) people with diabetes who were taking insulin. 271 had no retinopathy in either eye and 20% had proliferate diabetic retinopathy.[112] The mean duration of diabetes was 14 years and the mean HbA1c was 12.5%.
- Of the 271 persons with no retinopathy in either eye at baseline, 59% had some retinopathy at four years, and one (0.4%) had proliferative diabetic retinopathy. One patient with grade 21 retinopathy at baseline progressed to proliferative retinopathy with high-risk characteristics after four years (0.4%).

Baseline Retinopathy Severity (worst eye)	Progression to proliferative diabetic retinopathy	Progression to diabetic retinopathy with high-risk characteristics
No retinopathy (grade 10)	1/271 (0.4%)	0/271 (0%)
Microaneurysms only, or blot hemorrhages or soft exudates in the absence of microaneurysms (grade 21)	7/171 (4.1%)	0/171 (0%)
Microaneurysms and other retinal lesions (grade 31 to 51)	67/271 (25%)	28/271 (10.3%)

Diabetic Retinopathy (Without Macular Edema) in People With Diabetes ≥ Age 30

- The second study included 1,780 people with diabetes diagnosed at age 30 or older.[113] Of the insulin-taking patients, 32% had no retinopathy in either eye and 12% had proliferate diabetic retinopathy. The mean duration of diabetes was 14 years and the mean HbA1c was 11.8%. Of those who were not using insulin, 64% had no retinopathy in either eye, 2% had proliferate diabetic retinopathy. The mean duration of diabetes was eight years and the mean HbA1c was 10.2%.
- Results were similar for patients who used insulin at baseline, and those who did not (p = ns). Among persons with no retinopathy in either eye at baseline, the incidence of some retinopathy at four years was 34% among the 320 persons not using insulin at baseline, 47% among the 154 persons using insulin at baseline.
- This evidence suggests that there is a very low rate of progression over four years of a baseline of no retinopathy (grade 10) or grade 21 to proliferative diabetic retinopathy with or without high-risk characteristics.

Baseline Retinopathy Severity (worst eye)	Progression to proliferative diabetic retinopathy	Progression to diabetic retinopathy with high-risk characteristics
No retinopathy (grade 10)	2/474 (0.4%)	not reported
Microaneurysms only, or blot hemorrhages or soft exudates in the absence of microaneurysms (grade 21)	1/161 (0.6%)	not reported
Microaneurysms and other retinal lesions (grade 31 to 51)	67/269 (14%)	not reported

Diabetic Retinopathy (With Macular Edema) in the Entire Study Population

- The third study combined patients from the first two studies to evaluate the incidence of macular edema after four years (baseline characteristics described in previous bullets).[114]
- Presence of macular edema was defined as thickening of the retina with or without partial loss of transparency within one disc diameter (DD) of the center of the macula. Clinically significant macular edema was based on the detailed grading and was defined as the presence of any one of the following: thickening of the retina located 500 um or less from the center of the macula; or a zone of retinal thickening one disc area larger in size, located one DD or less from the center of the macula. Clinically significant macular edema (CSME) has been found to be associated with benefit from focal or grid laser treatment. Treatments at earlier stages of macular edema were not associated with benefit.
- The proportion of cases of macular edema that were judged clinically significant was 26/52 (52%) of persons under 30 years old at onset of diabetes and 19/34 (56%) of persons 30 years or older at onset of diabetes.

Baseline Retinopathy Severity (worst eye)	Progression to Macular Edema	
	age < 30 at onset of diabetes	age ≥ 30 at onset of diabetes
No retinopathy (grade 10)	3/286 (1.0%)	5/450 (1.1%)
Microaneurysms only, or blot hemorrhages or soft exudates in the absence of microaneurysms (grade 21)	15/150 (10%)	6/100 (6%)
Microaneurysms and other retinal lesions (grade 31 to 51)	29/158 (18%)	21/98 (21%)

- The evidence from these studies suggests that there is a very low rate of progression over four years from a baseline of no retinopathy (grade 10) or grade 21 to proliferative diabetic retinopathy with or without high-risk characteristics. There is an association with the development of proliferate diabetic retinopathy with high-risk characteristics for severe visual loss with a baseline of > 21 (i.e., ≥ 31).

Other Considerations

- The ADA recommends annual screening based upon patient expectations, the ability to detect other diseases and reinforce other diabetic messages, and known incomplete compliance with guidelines.[21]
- Cost/utility analysis of screening intervals cite that it may not be warranted to perform annual retinal screening on all patients without previously detected retinopathy with type 2 diabetes.[115] Tailoring recommending intervals based on individual circumstances may be preferable.
- HEDIS requires annual exams except if the patients meet two of the following three criteria: no evidence of retinopathy on a prior exam, HbA1c < 8%, are not on insulin.[109]
- A study underway in TPMG's Division of Research, reviewing ophthalmologist and optometrist visits for diabetic retinopathy screening, found that clinicians under-reporting of actual eye disease.[116] Level 21* was often entered when documentation clearly indicated greater degrees of retinopathy.

* Note: No retinopathy (grade 10). Microaneurysms only, blot hemorrhages, or soft exudates in the absence of microaneurysms (grade 21). Proliferate diabetic retinopathy with high-risk characteristics for severe visual loss with a baseline of > 21 (i.e., ≥ 31).

25. Foot Screening

25A The GDT recommends that all patients with diabetes should have a foot screening that includes a monofilament test. *Evidence-based: B*

25B Patients with an abnormal monofilament test are at a high risk for lower limb complications and are candidates for entry into a podiatry population-based foot care program, or equivalent. *Evidence-based: B*

Rationale:

Evidence for Recommendation 25: Fair

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

Supporting Evidence for Identification of High-Risk Feet with a Monofilament

- One prospective cohort study was found that evaluated the outcomes of identifying people with diabetes with high-risk feet.[117]
- Screening was based on sensation to the 5.07 monofilament, the presence of foot deformity, and a history of lower-extremity events.
- Three hundred and fifty eight Native Americans with diabetes were screened and stratified into four risk categories based on the screening results and followed for 32 months.
- The investigators found that plantar ulcer rate and amputations increased with the risk categories. The rate of plantar ulcer was 300 (OR = 78) for the highest risk group. There were 14 amputations in the two highest risk groups.

Supporting Evidence for Population-Based Foot Programs

- Two systematic reviews were found that included studies that screened for high-risk feet and randomized people into a high-risk foot program.[118, 119]
- The Health Technology Assessment systematic review[118] included one screening and intervention RCT[120] for patients with feet at high-risk of ulceration.
- 2,001 people with asymptomatic feet were recruited from an outpatient diabetes clinic. Screening included examination using Semmes-Weinstein monofilaments plus biothesiometry and palpation of foot pulses. Inclusion criteria for the foot program were foot deformities, a history of ulceration, or an Ankle Brachial Pressure Index* (ABPI) ≤ 0.75.
- Participants were randomized to usual care or a podiatry intervention. The intervention included weekly appointments with podiatry at a diabetic foot clinic, hygiene maintenance, support hosiery, protective shoes, and education about foot hygiene and inspection.

* The Ankle Brachial Pressure Index (ABPI) is a measure of the fall in blood pressure in the arteries supplying the legs and as such is used to detect evidence of blockages (peripheral vascular disease). It is calculated by dividing the systolic blood pressure in the ankle by the higher of the two systolic blood pressures in the arms. An ABPI of > 0.9 is considered normal.

- The incidence of ulcers progressing to amputation was 66% in the control group and 29% in the treatment group ($p = 0.006$; NNT = 2 based on calculations in the systematic review). The incidence of amputation (major and minor) was 2.3% (25/1,000) in the control group and 0.7% (7/1,001) in the intervention group ($p < 0.04$ total, $p < 0.01$ for major amputations, $p > 0.15$ for minor amputations).
- The Hunt systematic review[119] in Clinical Evidence included one systematic review[121] that included the previously described screening and intervention study [120] along with other studies that did not meet our inclusion criteria.

Other Considerations

- An unpublished study presented at the 2001 ADA Scientific Session implemented a population-based diabetic foot screening and treatment program.[122]
- Patients were screened over a 26-month period and were stratified based on risk.
- The program resulted in a 35.7% decrease in foot-related hospital admissions (from 5.3 per 1,000 members per year to 3.4 per 1,000 members per year).
- Total hospital days per 1,000 members were reduced by 70.7%.
- Amputation incidence per 10,000 people with diabetes at baseline was 125 compared with 37.5 per 10,000 after 26 months of follow-up (70% reduction).

26. Frequency of Foot Screening

26 The GDT recommends annual foot screenings for patients with diabetes.
Consensus-based

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

There is no evidence to recommend a frequency of foot screening.

Other Considerations

- The ADA recommends that a foot examination take place at routine follow-up visits in patients at risk. If abnormalities are identified, more frequent follow-up may be required.[21]
- The GDT recommended annual foot screening because it is an easy interval for the patient to remember and it is an opportunity to reinforce good foot care.

Self-Management

27. Self-Management Education

27 The GDT recommends patient training in self-care behaviors as a component of any diabetes management program.
Evidence-based: A – (Effect on Glucose Control)
Consensus-based – (Effect on Other Outcomes)

Rationale:

Evidence for Recommendation 27: Good

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

One meta-analysis was found that evaluated the efficacy of self-management education on GHb in adults with type 2 diabetes.

- Norris, et al. [123] compiled and analyzed literature between 1980 and 1999 and concluded that diabetes self-management education (DSME) significantly improves glycemic control in patients with type 2 diabetes. Increased contact time increases the effect.
- The intervention decreased GHb by 0.76% (95% CI: 0.34% to 1.18%) more than the control group at immediate follow-up.
- GHb decreased more with additional contact time between participant and educator, 1% decrease for every additional 23.6 hours of contact.
- This benefit declined one to three months after the intervention.

28. Self-Monitoring of Blood Glucose in Type 1 Diabetes

28A The GDT strongly recommends that patients with type 1 diabetes monitor their blood glucose. *Evidence-based: A*

28B The GDT strongly recommends that when self-monitoring of blood glucose (SMBG) is used, results be accompanied by an appropriate adjustment in therapy.
Evidence-based: A

Rationale:

Evidence for Recommendation 28: Good

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- There were no RCTs found that included long-term health outcomes for self-monitoring of blood glucose (SMBG). One systematic review was found that looked at the effect of SMBG on glucose control in people with type 1 diabetes.[124]
- Eight RCTs were included in the systematic review.[125, 126] Inclusion criteria varied per study. Sample size ranged from 16 to 69 and trial durations ranged from 24 weeks to two years.

- Frequency of testing varied per study and ranged from three times per day to two days within two weeks.
- Seven studies encouraged patients to change their therapy in response to their monitoring results.
- The review found the estimated absolute effect of blood monitoring on GHb* was -0.56% (95% CI: -1.073 to -0.061). Occurrence of hypoglycemia was low.
- UKPDS[85] and DCCT[84] found that lower HbA1c is associated with a lower risk of complications.
- There was moderate improvement in GHb using blood glucose monitoring in studies of people with type 1 diabetes where, in some studies, patients were encouraged to change therapy based on monitoring results. The focus of intense management seemed to change glucose control, not the SMBG itself.
- Overall, glucose monitoring may result in improved glucose control, although a change in management may be required for glucose monitoring to be effective.

Other Considerations

- The ADA recommends frequent SMBG (at least three or four times per day) for people with type 1 diabetes, in order to help achieve glycemic control and to prevent complications associated with tight control.[21]
- There is conflicting Kaiser Permanente internal data regarding the effect of increased frequency of monitoring glucose on HbA1c.
- KP Northern California published internal data in cohort design that showed self-monitoring of blood glucose three or more times per day was associated with lower HbA1c than less frequent monitoring in type 1 and 2 diabetes. In type 1 there was a 1.0 percentage point drop in HbA1c and a 0.6 percentage point drop in HbA1c in type 2 ($p < 0.0001$). Patients with type 2 diabetes who practiced self-monitoring at any frequency had a 0.4-point drop in HbA1c vs. no monitoring ($p < 0.0001$).[127]
- KP Georgia presented internal data at the 2001 ADA Scientific Session that showed daily self-monitoring of blood glucose significantly reduced HbA1c in both type 1 and 2 diabetes on insulin compared with those who monitored their glucose less than daily. There was no significant difference between groups in type 2 patients who were taking oral glucose lowering agents and those who were not on insulin.[128]
- SMBG is widely prescribed and practiced in diabetes. The role of SMBG in type 1 diabetes is fairly clear.

* GHb = all glycosylated hemoglobin, not hemoglobin HbA1c alone.

29. Self-Monitoring of Blood Glucose in Type 2 Diabetes

29A The GDT recommends self-monitoring of blood glucose (SMBG) for patients with type 2 diabetes. *Consensus-based*

29B When SMBG is used, the GDT recommends that results be accompanied by an appropriate adjustment in therapy. *Consensus-based*

Rationale:

2007 Update:

No new evidence was found, the recommendation remain unchanged.

2005 Update:

- There were no RCTs found that included long-term health outcomes for self-monitoring of blood glucose (SMBG). One systematic review was found that looked at (SMBG) in type 2 diabetes.[124]
- Eight RCTs were included in the systematic review.[129] Inclusion criteria varied per study. Sample size ranged from 27 to 108 and trial durations ranged from 16 to 52 weeks.
- The interventions included blood monitoring, urine monitoring, and no monitoring. The frequency of monitoring varied by study.
- No study required patients to modify their drug therapy in accordance with their self-monitoring results, although in some studies a physician made changes. Some studies encouraged patients to change their behavior or diet in response to the results of monitoring.
- One study showed a small but significant decrease in HbA1c, and four studies found a positive effect on GHb -0.25% (95% CI: -0.61 to 0.10). Three studies reported that neither urine nor blood testing affected blood glucose control. One study suggested blood and urine monitoring were equally efficacious. Four studies found no impact on health-related quality of life.
- Studies included in the systematic review had low statistical power and were poorly conducted and reported.
- The effect of self-monitoring in type 2 diabetes was half of what it was in type 1. There was a trend toward a small improvement in GHb although this was not statistically significant. It should be noted that in type 2 diabetes, none of the studies encouraged patents to modify therapy based on results of SMBG.

Other Considerations

- The ADA recommends daily SMBG for patients treated with insulin or sulphonylureas to monitor for and prevent asymptomatic hypoglycemia.[21]
- A structured questionnaire, NHANES III, and clinical and laboratory assessment were obtained on a national sample of people with type 2 diabetes. The data examined were therapy for diabetes, frequency of self-monitoring of blood glucose, and HbA1c values. Before the data were broken out into subcategories, it appeared that the amount of patients that tested their blood glucose increased with increasing HbA1c value. When the data were examined by therapeutic category, there was little correlation between HbA1c and testing at least once per day vs. testing at least once per week.[130]
- There are conflicting results from Kaiser Permanente internal data that increased frequency of monitoring glucose affects HbA1c.

- KP Northern California published internal data in cohort design that showed self-monitoring of blood glucose three or times per day was associated with lower HbA1c when compared with less frequent monitoring in type 1 and 2 diabetes.[127] In type 1 there was a 1.0 percentage point drop in HbA1c and a 0.6 percentage point drop in HbA1c in type 2 ($p < 0.0001$). Patients with type 2 diabetes who practiced self-monitoring at any frequency had a 0.4-point drop in HbA1c vs. no monitoring ($p < 0.0001$).
- KP Georgia presented internal data at the 2001 ADA Scientific Session that showed daily self-monitoring of blood glucose significantly reduced HbA1c in both type 1 and 2 diabetes receiving insulin compared with those who monitored their glucose less than daily.[128] There was no significant difference between groups in type 2 patients who were taking oral glucose lowering agents and those who were on insulin.
- The role of SMBG is less clear in people with type 2 diabetes than in type 1 diabetes. The evidence for SMBG in type 2 is not high-quality and is conflicting.

30. Self-Titration of Insulin

30 The GDT recommends self-titration of bedtime insulin dosage for patients with type 2 diabetes to enhance glucose control. *Evidence-based: B*

Rationale:

Evidence for Recommendation 30: Fair

Supporting Evidence:

- Two RCTs were identified that examined the effect of different approaches to self-titration of insulin therapy, and five other RCTs used self-titration in comparisons of different insulin preparations.
- A large, multicenter, four-armed factorial trial (Kennedy et al., 2006[131]) studied the effectiveness of a weekly self-titration algorithm according to (1) the intensity and frequency of reinforcement of the algorithm (weekly by phone, fax or e-mail compared with every six weeks at office visits) and (2) the lag in providing HbA1c levels to the patient within (1) two or three days compared with (2) every six weeks. For the primary endpoint of reduction in HbA1c levels, weekly reinforcement was more effective than reinforcement every six weeks, with reductions of 1.5% and 1.3%, respectively ($p < 0.001$). The timing of the provision of HbA1c levels was not associated with a significant difference in HbA1c levels.
- Davies et al.[132] reported the results of a large clinical trial that compared physician-led titration of bedtime insulin once a week to patient self-titration every three days [AT LANTUS study]. For the secondary endpoint of HbA1c, both groups achieved significant reductions in HbA1c, but self-titration was associated with a significantly greater reduction than physician-led titration (8.9 ±1.3 to 7.7 ±1.2%, and 8.9 ±1.3% to 7.9 ±1.2%, respectively ($p < 0.001$). There was no difference in the primary endpoint, frequency of severe hypoglycemia.
- Thus, in both cases, a more frequent "independent" (of the physician) activity (whether it was self-titration every three days[132] or reinforcement of the algorithm by a nurse every week[131]) was more effective than less frequent direct physician involvement (visit or phone call every week[132] or visit every six weeks[131]).
- The following five studies constitute "before-and-after" studies of self-titration, because random allocation pertained to some element of care other than self-titration.

- Gerstein et al.[133] compared the effect of 24 weeks of treatment with self-titrated daily insulin added to oral antidiabetic agents with the effect of treatment with physician-titrated oral antidiabetic agents [INSIGHT study]. Patients in the insulin group were significantly more likely to reach target levels of HbA1c than were patients in the group taking titrated oral agents only.
- Yki-Jarvinen et al.[98] reported the results of an RCT [LAN- MET study] comparing a titrated dosage of NPH insulin or glargine for adult patients whose type 2 DM was inadequately controlled by metformin therapy. Both groups achieved good glycemic control. During the first 12 weeks of the 36-week study, hypoglycemic events were more common in the glargine group, but this difference did not persist.
- A large, multicenter, randomized, open-label trial (Janka et al., 2005[134]) compared the effect of treatment with oral antidiabetic agents plus one daily injection of insulin glargine with the effect of a regimen including two daily injections of premixed insulin for insulin-naïve patients with poor glycemic control. Both groups titrated insulin dosages based on self-monitored blood glucose, and both achieved significant reductions in HbA1c, although the group receiving glargine plus oral medication had better HbA1C outcome.
- Raskin et al.[135] in the INITIATE study randomized insulin-naive study subjects to receive treatment with insulin glargine or biphasic insulin as part premixed 70/30 titrate, according to patient-instructed algorithms based on self-monitoring of blood glucose. Both groups demonstrated significant reduction in HgA1c with comparable incidence of hypoglycemia, but the 70/30 insulin group achieved better glycemic control.
- The Treat-To-Target trial (Riddle et al., 2003[136]) was a multicenter study comparing titrated treatment with bedtime glargine injection with titrated treatment with bedtime NPH insulin. Both groups achieved excellent results, but a significantly larger percentage of patients in the glargine group did so without documented evidence of nocturnal hypoglycemia (33.2 vs. 26.7%, $p < 0.05$.)

Overall Conclusion

There is fair evidence from multiple before-and-after studies that the benefits of self-titration of insulin substantially outweigh the harms and costs. In addition, there is fair evidence from two RCTs that greater patient autonomy with more frequent reinforcement or self-titration is more effective than less frequent direct physician involvement.

Appendix A: Criteria for Grading the Evidence

Label and Language of Recommendations

Revised: April 2008

RECOMMENDATION LABEL	RECOMMENDATION STATEMENT*	EVIDENCE BASE
Evidence-Based Recommendations		
Evidence-Based, A	The GDT strongly recommends the intervention.	The intervention improves important health outcomes, based on good evidence, and the Guideline Development Team (GDT) concludes that benefits substantially outweigh harms and costs.
Evidence-Based, B	The GDT recommends the intervention.	The GDT concludes that the intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs.
Evidence-Based, C	The GDT makes no recommendation for or against the intervention.†	Evidence is sufficient to determine the benefits, harms, and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. But the GDT concludes that the balance of the benefits, harms, and costs is too close to justify a general recommendation.
Evidence-Based, D	The GDT recommends against the intervention.	The GDT finds at least fair evidence that the intervention is ineffective, or that harms or costs outweigh benefits.
Evidence-Based, I	The GDT makes no recommendation for or against the intervention.†	The GDT concludes that evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined.
Consensus-Based Recommendations		
Consensus-Based	The GDT recommends the intervention.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Consensus-Based	The GDT has determined that the intervention is an option.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Consensus-Based	The GDT recommends against the intervention.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Note that most consensus-based recommendations will have evidence grade "Insufficient." For the rare consensus-based recommendations which have "Good" or "Fair" evidence, the evidence must support a different recommendation, because if the evidence were good or fair, the recommendation would usually be evidence-based.. In this kind of consensus-based recommendation the evidence label should point this out, e.g., "Good, supporting a different recommendation."		

* All statements specify the population for which the recommendation is intended.

†At the discretion of the GDT, the recommendation may use the language, "option," but must list all the equivalent options.

KP System for Grading the Strength of a Body of Evidence

Level/Grade	Therapy/Prevention/Screening	Diagnosis	Prognosis/Etiology
Grade GOOD	**Type and number of studies** ▪ At least one well-designed and conducted systematic review (SR)/meta-analysis (MA) (consider heterogeneity) of RCTs ▪ Two or more well-designed and conducted RCTs with narrow confidence intervals ▪ One well-designed and conducted multi-center RCT with narrow confidence intervals **Quality** ▪ Low risk of bias ▪ Adequate sample size and power ▪ No major methodological concerns **Consistency** ▪ For SR/MA, no major conflict in results (consider heterogeneity). If significant heterogeneity exists, drops to Poor ▪ For individual RCTs, no major conflict in results ▪ If major conflicts do exist, drop to "Insufficient" **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population	**Type and number of studies** ▪ At least one well-designed and conducted SR/MA (consider heterogeneity) of cross-sectional studies using independent gold standard ▪ Two or more well-designed and conducted cross-sectional studies using an independent gold standard **Quality** ▪ Low risk of (verification) bias ▪ Independent gold standard ▪ No major methodological concerns **Consistency** ▪ For SR/MA no major conflict in results (consider heterogeneity) ▪ For individual studies, consistent diagnostic accuracy **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population	**Type and number of studies** ▪ At least one well-designed and conducted SR/MA (consider heterogeneity) of prospective cohort studies ▪ Two or more well-designed and conducted prospective cohort studies **Quality** ▪ Low risk of bias ▪ Acceptable loss to follow-up (< 20%) ▪ No major methodological concerns **Consistency** ▪ For SR/MA no major conflict in results (consider heterogeneity) ▪ For individual studies, consistent prognosis in similar populations **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population
Grade FAIR	**Type and number of studies** ▪ Single well-designed and conducted RCT with narrow confidence intervals ▪ Two or more RCTs of lower quality ▪ Well-designed and conducted SR/MA of cohort studies (consider heterogeneity) *For screening interventions only, the following are also acceptable as Fair evidence:* ▪ Two or more well-designed and conducted cohort studies ▪ Two or more well-designed and conducted case-control studies ▪ Two or more well-designed and conducted time series studies **Quality** ▪ Minor methodological concerns **Consistency** ▪ For SR/MA, no major conflict in results (consider heterogeneity) ▪ For individual studies, no major conflict in results ▪ If major conflicts do exist, drop to "Insufficient" **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population	**Type and number of studies** ▪ Single well-designed and conducted cross-sectional study ▪ Two or more cross-sectional studies of lower quality ▪ Well-designed and conducted SR/MA of lower quality studies **Quality:** ▪ Minor methodological concerns ▪ Independent gold standard **Consistency:** ▪ For SR/MA, no major conflict in results (consider heterogeneity) ▪ For individual studies, no major conflict in results **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population	**Type and number of studies** ▪ Single well-designed and conducted prospective cohort study ▪ Two or more prospective cohort studies of lower quality ▪ Well-designed and conducted SR/MA (consider heterogeneity) of either retrospective cohort studies, case control or untreated control arms in RCTs *For etiology only, the following is also acceptable as Fair evidence:* ▪ Two or more well-designed, well-conducted retrospective cohort studies ▪ Two or more well-designed, well-conducted case control studies, preferably confirmed by one or more cohort studies **Quality:** • Minor methodological concerns **Consistency:** ▪ For SR/MA, no major conflict in results (consider heterogeneity) ▪ For individual studies, no major conflict in results **Relevancy** ▪ No compelling reason not to generalize the published work to the target KP population
Grade INSUFFICIENT *NOTE: Any evidence that fails to meet criteria for GOOD or FAIR evidence is considered to be INSUFFICIENT. Examples of insufficient evidence are provided for the different criteria.*	**Type and number of studies** ▪ Single RCT of lower quality or insufficient size ▪ Cohort study **Quality** ▪ Major methodological concerns (i.e., lack of concealed allocation, inadequate blinding, no ITT analysis) **Consistency** ▪ Studies that are well-designed and conducted (Good or Fair) but with major conflict in results ▪ SR/MA with major conflict in results (consider heterogeneity) **Relevancy** ▪ Compelling reasons why the results do not apply to the target KP population	**Type and number of studies** ▪ Single cross-sectional study of lower quality ▪ Case-control study **Quality** ▪ Major methodological concerns (non-consecutive, poor or non-independent gold standard) **Consistency** ▪ Studies that are well-designed and conducted (Good or Fair) but with major conflict in results **Relevancy** ▪ Compelling reasons why the results do not apply to the target KP population	**Type and number of studies** ▪ Single prospective cohort study of lower quality ▪ Retrospective cohort study ▪ Untreated control arm of RCT ▪ Case series **Quality** ▪ Major design or methodological concerns (sampling bias, high dropout, non-blinded outcome assessment, lack of adjustment for confounders) **Consistency** ▪ Studies that are well-designed and conducted (Good or Fair) but with major conflict in results **Relevancy** ▪ Compelling reasons why the results do not apply to the target KP population

*Evidence is graded with respect to the degree it supports the specific clinical recommendation. For example, there may be good evidence that Drugs 1 and 2 are effective for Condition A, but no evidence that Drug 1 is more effective than Drug 2. If the recommendation is to use either Drug 1 or 2, the evidence is good. If the recommendation is to use Drug 1 in preference to Drug 2, the evidence is insufficient.

Appendix B: Supporting Documentation

Prevention of Diabetes

Intervention to Delay the Onset of Type 2 Diabetes

Problem Formulation 1

Clinical Question:	Is there an intervention that can delay the onset of diabetes in people with impaired glucose control?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals on who, when, and how to delay the onset of diabetes
Population:	All adults
Health Problem:	Development of type 2 diabetes
Health Intervention:	▪ Lifestyle interventions ▪ Drug therapy intervention ▪ Combination therapy (lifestyle plus medication) ▪ No intervention
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Delayed onset of diabetes ▪ Delayed diabetes complications ▪ Improved functional /health status ▪ Improved quality of life ▪ Decreased mortality ▪ Decreased hospitalization ▪ Decreased office visits
Side Effects of the Intervention:	▪ Quality of Life ▪ Functional health status ▪ Gastrointestinal (GI) upset

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved*
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/30/2007	1/117
	"Diabetes Mellitus, Non-Insulin-Dependent/prevention and control"[MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	2001 – 07/30/07	2/102
	"Diabetes Mellitus, Non-Insulin-Dependent/prevention and control"[MAJR] AND ("glucose intolerance/complications"[MESH] OR "glucose intolerance/drug therapy"[MESH] OR "glucose intolerance/therapy"[MESH])	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 09/04/01	4/7
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Vol. 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Evidence Tables

Table 1.1: Interventions For Delaying the Onset of Type II Diabetes

Study, Total N	Study Population Treatment Groups & Drug	Results	Comments
Lifestyle Education for Prevention of DM			
Yamaoka K, Tango T (2005) Meta-Analysis **# studies found:132** **# studies included: 9** **Total N 5260**	Randomized trials which followed patients for ≥ 6 months for lifestyle changes including diet and exercise or solely dietary education interventions 7 comparisons of dietary and exercise interventions 2 comparisons of dietary interventions alone	**Outcomes of Interest:** 1-year lifestyle education intervention reduced 2-h plasma glucose by 0.84 mmol/l (95% CI 0.39-1.29) Risk of incidence of type 2 diabetes in the lifestyle education intervention group was reduced by ~ 50% (RR=0.55 [95% CI 0.44-0.69]) compared with the control intervention group.	**Reported Conclusions:** Lifestyle education was effective for reducing both 2-h plasma glucose and relative risk of developing DM in high-risk individuals.. **Limitations:** Interventions and lifestyle-change methods varied. Dietary interventions included dietary counseling, reduced-fat diet, small-group education, and weight reduction through a low-calorie, low-fat diet. Exercise interventions included education in increasing leisure physical activities at least 1 unit/day, regular exercise program, physical activity counseling, and circuit- type resistance training sessions.

Table 1.2: Lifestyle vs. Placebo

Study, Total n	Treatment Groups Size and Drug	Study Population	Results	Comments
Pan XR, et al. **Effects of Diet and Exercise in Prevention NIDDM in People with Impaired Glucose Tolerance: The Da Quing IGT and Diabetes Study**. Diabetes Care 1997: 20(4); 537-544 (6) **Location:** China **Sponsor:** Not stated	Groups: C: General information about diabetes and impaired glucose tolerance, informational brochures with instructions for diet and/or increased leisure physical activities (no individual instruction or formal group counseling sessions) Rx1: Diet-only intervention where participants with BMI <25kg/m^2 prescribed a diet with 25-20 kcal/kg body weight, 55-65% carbohydrate, 10-15% protein and 25-30% fat. Participants with BMI =25kg/m^2 were encouraged to reduce calorie intake to gradually lose weight at a rate of 0.5-1.0 kg per month until they achieved a BMI=23kg/m^2. Patients received individual counseling regarding daily food intake and counseling sessions weekly for 1 month, monthly for 3 months and then once every 3 months for the rest of the study. Rx2: Increased exercise by at least 1U/day (mild, moderate, strenuous or very strenuous) and by 2U/day for those age <50 with no evidence of cardiovascular disease of arthritis. Counseling sessions were also held. Rx3: Diet plus exercise group received instructions and counseling for both diet and exercise interventions.	Inclusion criteria: 110,660 people over age 25 were screened for a plasma glucose concentration 2 hours after a standard breakfast, followed by a 75g oral glucose tolerance test who were screened positive Exclusion criteria: not stated Baseline data: 208 had BMI <25kg/m2, 322 were overweight (=25kg/m2), mean age 45.0±9.1, 283 male, 247 female Initial N: 577 Final N: 530 C: 133 Rx1: 130 Rx2: 141 Rx3: 126	Outcomes of interest Total incidence of diabetes: C: 67.7% (59.8, 75.2) Rx1: 43.8% (35.5, 52.3) Rx2: 41.1% (33.4, 49.4) Rx3: 46.0% (37.3, 54.7) p<0.05 for all comparisons with control Incidence rate (100 person-years) of diabetes in people with BMI <25kg/m2: C: 13.3 (8.9, 17.7) Rx1: 8.3 (4.9, 11.7) Rx2: 5.1 (2.6, 7.6) Rx3: 6.8 (3.6, 10.0) p=ns for C vs. Rx1 p<0.01 for C vs. Rx2 p=0.05 for C vs. Rx3 Incidence rate (100 person-years) of diabetes in people with BMI =25kg/m2: C: 17.2 (13.3, 21.3) Rx1: 11.5 (8.0, 15.0) Rx2: 10.8 (7.8, 13.8) Rx3: 11.4 (8.1, 14.6) p<0.05 for all comparisons with control	Biases Small N Clinic randomization rather than individual randomization Local physicians, nurses, and technicians trained on instruction on diet and exercise interventions, and procedures for the exams (train the trainer)

Table 1.3: Lifestyle vs. Placebo

Study, Total n	Treatment Groups Size and Drug	Study Population	Results	Comments
Tuomilehto J, 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): 1343-1350 [7] **Location:** Finland in 5 study centers **Sponsor:** The Finnish Academy, The Ministry of Education, The Novo Nordisk Foundation, The Yrjo Jahnsson Foundation, The Finnish Diabetes Research Foundation. Initial N: C: 257 Rx: 265 Final N: C: 250 Rx: 256	Groups: C: Oral and written information about diet (2 page leaflet) and exercise at baseline/annual visits with no specific individualized programs offered to them. Completed 3-day food diary at baseline/annual visit using a booklet to illustrate portion sizes. Rx: individualized counseling aimed at reducing weight, total intake of fat and intake of saturated fat and increasing intake of fiber and physical activity Goals of the program: Weight reduction: 5% or >\ Total Fat Intake: <30% of energy consumed Saturated Fat Intake: <10% of energy consumed Increase fiber intake to: 15gm/1000kcal Moderate exercise for at least 30 minutes/day Dietary advice tailored to each patient. Received individual guidance on increasing their level of physical activity.	**Inclusion criteria:** middle-aged (age 40-65) overweight subjects (BMI>25) with impaired glucose tolerance (plasma glucose concentration of 140-200 mg/dl, or 7.8-11.0 mmol/l, two hours after oral administration of 75g glucose) (patients were recruited through screening of high-risk groups such as first degree relatives of patients with type 2 Diabetes) **Exclusion criteria:** diagnosis of diabetes, presence of chronic disease which may limit survival to under 6 years, psychological or physical disabilities **Baseline data:** 172 men, 350 women, mean age 55, mean BMI 31, mean fasting plasma glucose 123 mg/dl, Mean plasma glucose 2 hrs after oral challenge: 158 mg/dl	Outcomes of Interest Mean weight lost after year 1: C: 0.8±3.7 kg Rx: 4.2±5.1 kg p<0.001 Mean weight lost after year 2: C: 0.8±4.4 kg Rx: 3.5±5.5 kg p<0.001 Cumulative incidence of diabetes after 4 years: C: 23% (17, 29) Rx: 11% (6, 15) Risk reduced by 58% p<0.001 Change in fasting plasma glucose (mg/dl): C: 1±12 (0,2) Rx: -4±12 (-6,-2) p<0.001 Change in plasma glucose(mg/dl) 2hr after oral glucose challenge: C: -5±40 (-8, 2) Rx: -15±34 (-19,-11) p=0.003	**Biases** Small N 15 patients withdrew during the first year Information about patient health behavior during the study was based on subjective data from patients rather than objective evaluation by evaluators

Table 1.4: Metformin vs. Placebo

Study, Total n	Treatment Groups Size and Drug	Study Population	Results		Comments
Li CL, et al. **Effect of metformin on patients with impaired glucose tolerance**. Diabetic Medicine 1999: 16; 477-481 [8] **Location:** China **Sponsor:** Not stated	**Groups:** C: placebo Rx: metformin (250 mg 3x/daily) **Initial N:** 70 C: 37 Rx: 33 **Final N:** Not stated **Compliance:** 5 patients lost to follow-up	**Inclusion criteria:** employees of Shougang Corporation age 30-60, with IGT (WHO definition) found using a 75g oral glucose test. **Exclusion criteria:** pre-existing diabetes, history of ischemic heart disease, renal, hepatic disorders, patients previously treated with metformin **Baseline data:** 50 males, 20 female, mean age about 50, mean BMI about 26	**Total incidence of diabetes:** C: 16.2% Rx: 3.0% p=0.011	**Percent of patients reverted to normal glucose tolerance:** C: 51.4% Rx: 84.9% p=0.011	**Biases** Small N

Table 1.5: Metformin vs. Lifestyle

Study, Total n	Treatment Groups Size and Drug	Study Population	Results		Comments
Knowler WC. **Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin.** N Engl J Med 2002; 346:393-403 [5] The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. Diabetes Care. 2000;23(11);1619-29 [16] **Location:** 27 centers nationwide **Sponsor:** Mainly funded by the NIH. Funded in part through a Cooperative Research Development Agreement (CRADA) with Bristol Myers Squibb. Other sources of corporate support include Merck and Company, Merck Medco, Hoechst Marion Roussell, Lifescan, Slimfast, Nike, and Health-O-Meter.	Type of Design: RCT Blinding: Not stated Follow-up: 2.8 years (the trial ended a year early due to efficacy of the program) **Initial N:** 3234 C: 1082 Rx1: 1073 Rx2: 1079 **Final N:** 92.5% attended a scheduled visit within the five months prior to the end of the study	**Inclusion criteria:** Age 25 or older, overweight people (BMI =22kg/m2 for Asian-Americans) with impaired glucose tolerance (glucose 5.3-6.9 mmol/l or =6.9 mmol/l for American Indians), groups known to be at higher risk for type 2 diabetes (age 60 and older, women with a history of gestational diabetes, and people with a first-degree relative with type 2 diabetes) **Exclusion criteria**: not stated Baseline data: average BMI 34 age 25 to 85 with an average age of 51, 45% percent from minority groups (American Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians)	**Cumulative incidence of diabetes:** C: 29% Rx1: 14% Rx2: 22% Risk reduced by 58% (48, 66) for C vs. Rx1 (NNT 6.9) Risk reduced by 31% (17, 43) for C vs. Rx2 (NNT 13.9) Risk reduced by 39% (24, 51) for Rx1 vs. Rx2	**Percent of patients who achieved study weight loss by the end of the study:** C: not stated Rx1: 55% Rx2: not stated	**Biases** Study not published

Table 1.6: Acarbose vs. placebo

Study, Total n	Treatment Groups Size & Drug	Study Population	Results	Comments
Chiasson,JL, R G Josse, R Gomis, M Hanefeld, A Karasik, M Laakso, 2003, Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial: JAMA, vs. 290, p. 486-494. (RCT) Follow-up: 3 years **Initial N:** 1429 **Final N:** 1368 Sponsor Bayer AG	**Rx1** treatment (n=715) Placebo **Rx2** treatment (n=714) 100mg of Acarbose 3 times a day All patients were instructed on weight-reduction or weight-maintenance diet, and encouraged them to exercise regularly All participants met with a dietician before randomization and yearly thereafter Patients completed a 3-day nutritional diary at time of eating and recorded their physical activities during the 3 days (2 weekdays, I weekend) in the last month before each yearly visit	Inclusion criteria: IGT (7.8 mmol/L or greater and less than 11.1 mmol/L after a 75 g glucose load) Fasting plasma concentration levels of 5.6-7.7 mmol/L Ages of 40 to 70 years old BMI between 25-40 kg/m2 Patients were mainly recruited though screening of a high-risk population and in particular from first-degree relatives of patients with type 2 diabetes. Baseline data: Average age was 54.3 in Rx2 and 54.65 in Rx1. BMI in Rx1 was 30.9 and in Rx2 was 31.0	Effect of acarbose on development of diabetes **Acarbose Placebo HR p** **Overall** 221/682(32%) 285/686 (42%) 0.75(0.63-0.90) .0015 **Age(yrs)** ≤ 55 128/370 (35%) 147/354 (42%) 0.79 (0.6201.0) .0559 >55 92/311 (30%) 137/329 (42%) 0.70 (0.53-0.91) .0084 **Sex** Men 11/329 (34%) 144/344 (42%) 0.77 (0.60-0.99) .0382 Women 110/353(31%) 141/342 (41%) 0.71 (0.56-0.92) .0089 **BMI** ≥30 312/361 (37%) 163/368 (44%) 0.77 (0.61-0.97) .0269 <30 89/321 (28%) 121/318 (38%) 0.70 (0.53-0.92) .0115 NNT= 11 to delay the onset of diabetes by 3.3 years Weight loss contributed to the decreased risk of diabetes (p<.00001) but treatment with acarbose decreased the risk of diabetes even after adjustment for change in weight (p=.0063) BMI significantly affected development of diabetes (p 0.0066) whereas age and sex did not (p=ns) The probability of reverting to normal glucose tolerance over time was significantly higher in patients on acarbose than in those on placebo (p<0.0001) **Adverse events** Acarbose Placebo GI 83% 60% Flatulence 68% 27% Diarrhea 32% 17% Abdominal pain 17% 12%	Conclusions Intervention with acarbose in patients with impaired glucose tolerance delayed progression to type 2 diabetes when compared with placebo. Acarbose when compared with placebo resulted in more gastrointestinal side effects (flatulence, diarrhea, or abdominal cramps) Bias Used block randomization

Table 1.7: Orlistat vs. placebo vs. lifestyle

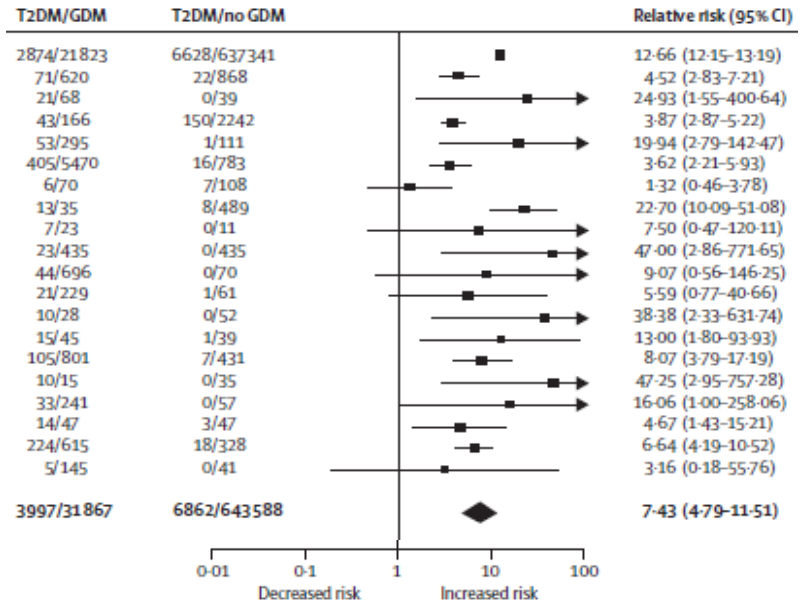
Study, Total n	Treatment Groups Size & Drug	Study Population	Results	Comments
Heymsfield SB, Segal KR, Hauptman J, Lucas CP, Boldrin MN, Rissanen A et al. **Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults**. Arch Intern Med 2000; 160(9):1321-1326. Follow-up: 582 days Initial N: 675 Final N: 463 (Pooled analysis of three 2-year randomized placebo-controlled clinical trials) Sponsor Hoffman-LaRoche	**Rx1** treatment (n=316) Placebo plus low-energy diet 3 times daily **Rx2** treatment (n=359) Orlistat, 120 mg plus low energy diet 3 times daily All patients were given a low-energy diet that provided 30% of energy intake a fat during a 4-week, single-blind placebo lead-in period. Weight change during the lead-in period used to evenly distribute between treatment groups, those who lost less than 2 kg vs. 2 kg or more. Energy intake in year 1 was prescribed for each patient on the basis of his or her estimated daily maintenance energy requirement (1/3Xcalculated basal metabolic rate) minus 2083 to 3333/kJ/d (500-800 kcal/d). During year 2, a weight maintaining diet was prescribed.	Inclusion criteria: Obese adults (BMI 30-43 kg/m2) Absence of weight loss in the previous 3 months Exclusion criteria: Stopped smoking within the past 6 mos Significant cardiac, renal, hepatic, GI, psychiatric, or endocrine disorders Drug-treated type 2 DM History of substance abuse Concomitantly used medications that alter appetite or lipid levels	Outcomes of interest Weight Loss Rx1: 3.9% ± 0.4% Rx2: 6.8% ± 0.4% P<.001 Change in Oral Glucose Tolerance Status from Baseline to End of Treatment Status at Endpoint, No. of subjects (%) Baseline / Treatment / Normal / Impaired / Diabetic / p* Normal / Placebo / 219(88.0) / 27(10.8) / 3(1.2) / .04 Orlistat / 255(93.4) / 18(6.6) / 0(0) / " Impaired / Placebo / 26 (49.1) / 23(43.3) / 4(7.6) / .04 Orlistat / 48(71.7) / 17(25.4) / 2(3.0) / " Diabetic / Placebo / 2(14.3) / 2(14.3) / 10(71.4) / .19 Orlistat / 3(15.8) / 8(42.1) / 8(42.1) / " *refers to significance of chi-square for distribution of end point status within each category of baseline status	**Conclusion**: Addition of orlistat to a conventional weight loss regimen significantly improved oral glucose tolerance and diminished the rate of progression to the development of type 2 diabetes **Limitations**: retrospective meta-analysis of glucose tolerance data

Table 1.8: 2009

Name Design	N	Mean Characteristics	Mean follow-up (SD or 95% CI)	Mean Duration of Intervention	Biases*	Results
Ratner 2008 RCT *Note that this is indirect evidence*	Total N=2190 **GDM cohort N=350** Placebo: 122 Metformin: 111 Intensive lifestyle: 117	**Before Intervention** **HbA1c:** 5.87±0.50 **Fasting glucose:** 105.8±8.4 mg/dl **BMI:** 34.2±6.2	NA	3 years	3,4	See nested table below
Bellamy et al. 2009 Meta-Analysis 20 cohort studies *Note that this is indirect evidence*	Total N: 675,455 History of GDM: 31,867 Incident cases of type 2 DM: 10,859	**Mean Maternal Age Study (years; SD or 95% CI of women with GDM/no GDM)** 1. 29.3 (5.5) 2. 33.6 (4.8) 3. 33.1/30.0 (5.9) 4. Matched range 18-30 5. 27.0 (5.1)/30.5(4.6) 6. 30.7 (5.1)/30.5 (4.6) 7. 26.9/25.1 8. matched age range 9. 32/27 (7) 10. 31.6 (17.7-46.5)/ 31.3 (18.8-46.0) 11. 30.7/30.4 12. matched age range 20-45 13. 32.6/30.6 14. 29/29 (23-40) 15. 34.0(4.1)/34.4(6.4) 16. 31.3(2.0)/36.0(0.9) 17. 30.1/26.7 18. 27.2/26.5 19. NA 20. 31(20-46)/30 (16-43)	1. 5.2 yrs 2. 2.1 yrs 3. 3.6 yrs (GDM 0.8)/8.1 yrs (non GDM 5.1) 4. 20 yrs (72% followed for entire time) 5. 6.75 yrs (0.8) 6. 2.2 yrs (GDM; 8.6 yrs (nonGDM) 7. 6.2 yrs (0.8) 8. 5 yrs 9. 16-24 wks 10. 5.7 yrs (GDM 1.0-11.6); 6.1 (nonGDM 1.5-13.1) 11. 6.16 yrs (0.05-13.73) 12. 1 yr 13. 15 yrs 14. 5-11 yrs 15. 6 wks 16. 7 yrs 17. 7.5 yrs 18. 4.8 yrs (GDM)/5.5 yrs (nonGDM 19. 22-28 yrs 20. 3-4 yrs	NA	2,3	See image below

	Placebo	Metformin	Intensive Lifestyle Treatment (ILS)
Incidence of DM (# of cases/100 person-years[a])	GDM: 15.2[b] no GDM: 8.9	GDM: 7.8 no GDM: 7.8	GDM: 7.4
Reduction in incidence (compared with placebo)[a]		GDM: 50.4[c] no GDM: 14.4	GDM: 53.4[c] no GDM: 49.2
NNT (to prevent one case in 3 yr compared with placebo)[a]		GDM: 6.1 no GDM: 21.0	GDM: 5.3 no GDM: 9.0

[a] Adjusted for age, [b] P<0.05 compared with non-GDM group, [c] P<0.05 compared with placebo



1: Sample attrition >15%; 2: Sample selection bias; 3: Detection bias (e.g., measurement error, ITT analysis, : Omitted variable bias; 5: Publication bias

Postpartum Screening for Diabetes in Women with a History of Getstational Diabetes Mellitus (GDM)

Problem Formulation 2

Clinical Question:	Is screening for diabetes recommended for women who have been diagnosed with gestational diabetes mellitus (GDM)?
Population:	Women who have been diagnosed with GDM
Health Intervention:	▪ Screening ▪ No Screening
Most Important Health Outcomes:	▪ Prevention of diabetes ▪ Prevention of diabetes complications

Search Strategy

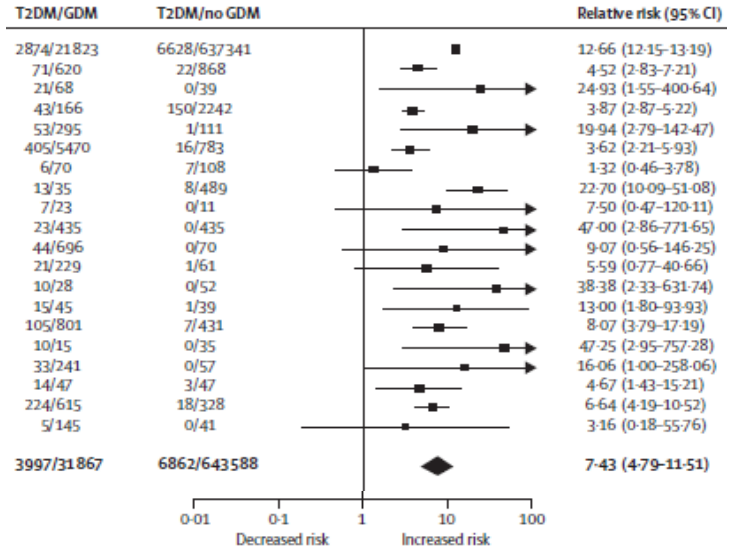
Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed. Additional evidence identified by a manual search.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH] ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07-09/4/09	1/65
	[MeSH] AND "Diabetes, Gestational"[MeSH] ("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields])) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07-09/4/09	1/3
		Randomized, controlled trial, All Adult: 19+ years English, Human	8/08/07-09/4/09	0/25
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05-09/4/09	0/67
Clinical Evidence	No terms used - searched book section Endocrine and Metabolic Disorders, Conditions: Diabetes, Pregnancy and Childbirth	Systematic reviews and RCTs	7/15/05-09/4/09	0/0

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/08/07	0/117
	"Follow-Up Studies" [MeSH] AND "Diabetes, Gestational"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/08/07	0/0
		Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 8/08/07	0/2
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Evidence Table

Table 2.1

Name Design	N	Mean Characteristics	Mean follow-up (SD or 95% CI)	Mean Duration of Intervention	Biases*	Results
Ratner 2008 RCT *Note that this is indirect evidence*	Total N=2190 **GDM cohort N=350** Placebo: 122 Metformin: 111 Intensive lifestyle: 117	**Before Intervention** **HbA1c:** 5.87±0.50 **Fasting glucose:** 105.8±8.4 mg/dl **BMI:** 34.2±6.2	NA	3 years	3,4	**Placebo** / **Metformin** / **Intensive Lifestyle Treatment (ILS)** Incidence of DM (# of cases/100 person-years[a]): GDM: 15.2[b], no GDM: 8.9 / GDM: 7.8, no GDM: 7.8 / GDM: 7.4 Reduction in incidence (compared with placebo)[a]: GDM: 50.4[c], no GDM: 14.4 / GDM: 53.4[c], no GDM: 49.2 NNT (to prevent one case in 3 yr compared with placebo)[a]: GDM: 6.1, no GDM: 21.0 / GDM: 5.3, no GDM: 9.0 [a] Adjusted for age, [b] P<0.05 compared with non-GDM group, [c] P<0.05 compared with placebo
Bellamy et al. 2009 Meta-Analysis 20 cohort studies *Note that this is indirect evidence*	Total N: 675,455 History of GDM: 31,867 Incident cases of type 2 DM: 10,859	**Mean Maternal Age Study (years; SD or 95% CI of women with GDM/no GDM)** 1. 29.3 (5.5) 2. 33.6 (4.8) 3. 33.1/30.0 (5.9) 4. Matched range 18-30 5. 27.0 (5.1)/30.5(4.6) 6. 30.7 (5.1)/30.5 (4.6) 7. 26.9/25.1 8. matched age range 9. 32/27 (7) 10. 31.6 (17.7-46.5)/ 31.3 (18.8-46.0) 11. 30.7/30.4 12. matched age range 20-45 13. 32.6/30.6 14. 29/29 (23-40) 15. 34.0(4.1)/34.4(6.4) 16. 31.3(2.0)/36.0(0.9) 17. 30.1/26.7 18. 27.2/26.5 19. NA 20. 31(20-46)/30 (16-43)	1. 5.2 yrs 2. 2.1 yrs 3. 3.6 yrs (GDM 0.8)/8.1 yrs (non GDM 5.1) 4. 20 yrs (72% followed for entire time) 5. 6.75 yrs (0.8) 6. 2.2 yrs (GDM; 8.6 yrs (nonGDM) 7. 6.2 yrs (0.8) 8. 5 yrs 9. 16-24 wks 10. 5.7 yrs (GDM 1.0-11.6); 6.1 (nonGDM 1.5-13.1) 11. 6.16 yrs (0.05-13.73) 12. 1 yr 13. 15 yrs 14. 5-11 yrs 15. 6 wks 16. 7 yrs 17. 7.5 yrs 18. 4.8 yrs (GDM)/5.5 yrs (nonGDM 19. 22-28 yrs 20. 3-4 yrs	NA	2,3	
				1: Sample attrition >15%; 2: Sample selection bias; 3: Detection bias (e.g., measurement error, ITT analysis, : Omitted variable bias; 5: Publication bias		

Postpartum Follow-up of GDM

Problem Formulation 3

Clinical Question:	What are the appropriate postpartum interventions for women who have had gestational diabetes mellitus (GDM) to prevent future development of type 2 diabetes mellitus (DM)?
Population:	Women who have had GDM
Health Intervention:	▪ Lifestyle interventions ▪ Drug therapy intervention ▪ Combination therapy (lifestyle plus medication) ▪ No intervention
Most Important Health Outcomes:	▪ Prevention of diabetes ▪ Prevention of diabetes complications

Search Strategy

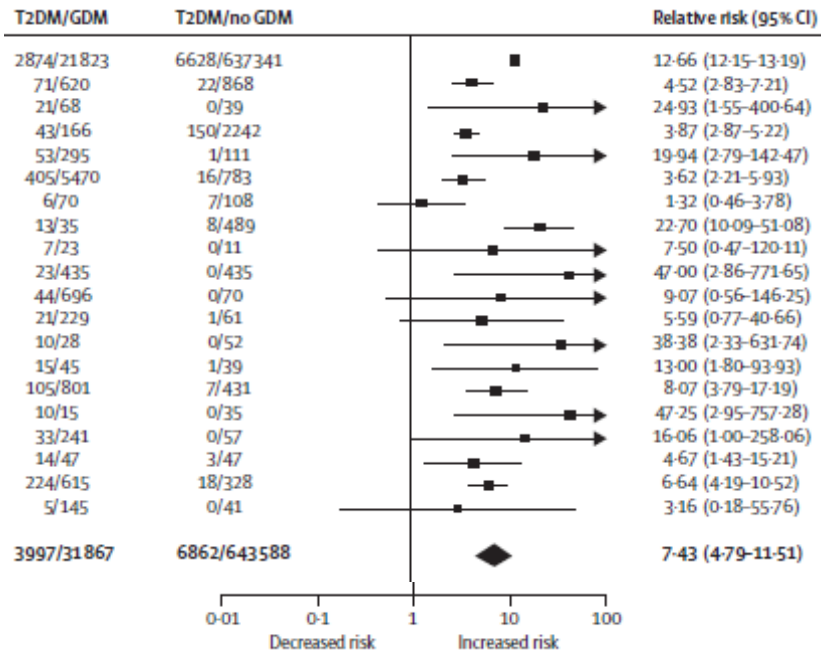
Additional evidence identified by a manual search.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH] ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07-09/4/09	0/65
	[MeSH] AND "Diabetes, Gestational"[MeSH] ("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields])) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07-09/4/09	0/3
		Randomized, controlled trial, All Adult: 19+ years English, Human	8/08/07-09/4/09	1/25
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05-09/4/09	0/67
Clinical Evidence	No terms used - searched book section Endocrine and Metabolic Disorders, Conditions: Diabetes, Pregnancy and Childbirth	Systematic reviews and RCTs	7/15/05-09/4/09	0/0

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/08/07	0/117
	"Follow-Up Studies" [MeSH] AND "Diabetes, Gestational"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/08/07	0/0
		Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 8/08/07	0/2
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Evidence Table

Table 3.1

Name Design	N	Mean Characteristics	Mean follow-up (SD or 95% CI)	Mean Duration of Intervention	Biases*	Results
Ratner 2008 RCT *Note that this is indirect evidence*	Total N=2190 **GDM cohort N=350** Placebo: 122 Metformin: 111 Intensive lifestyle: 117	**Before Intervention** **HbA1c:** 5.87±0.50 **Fasting glucose:** 105.8±8.4 mg/dl **BMI:** 34.2±6.2	NA	3 years	3,4	**Placebo** / **Metformin** / **Intensive Lifestyle Treatment (ILS)** Incidence of DM (# of cases/100 person-years[a]): GDM: 15.2[b] no GDM: 8.9 / GDM: 7.8 no GDM: 7.8 / GDM: 7.4 Reduction in incidence (compared with placebo)[a]: / GDM: 50.4[c] no GDM: 14.4 / GDM: 53.4[c] no GDM: 49.2 NNT (to prevent one case in 3 yr compared with placebo)[a]: / GDM: 6.1 no GDM: 21.0 / GDM: 5.3 no GDM: 9.0 [a] Adjusted for age, [b] P<0.05 compared with non-GDM group, [c] P<0.05 compared with placebo
Bellamy et al. 2009 Meta-Analysis 20 cohort studies *Note that this is indirect evidence*	Total N: 675,455 History of GDM: 31,867 Incident cases of type 2 DM: 10,859	**Mean Maternal Age Study (years; SD or 95% CI of women with GDM/no GDM)** 1 29.3 (5.5) 2 33.6 (4.8) 3 33.1/30.0 (5.9) 4 Matched range 18-30 5 27.0 (5.1)/30.5(4.6) 6 30.7 (5.1)/30.5 (4.6) 7 26.9/25.1 8 matched age range 9 32/27 (7) 10 31.6 (17.7-46.5)/ 31.3 (18.8-46.0) 11 30.7/30.4 12 matched age range 20-45 13 32.6/30.6 14 29/29 (23-40) 15 34.0(4.1) / 34.4(6.4) 16 31.3(2.0)/36.0(0.9) 17 30.1/26.7 18 27.2/26.5 19 NA 20 31(20-46)/30 (16-43)	1 5.2 yrs 2 2.1 yrs 3 3.6 yrs (GDM 0.8)/8.1 yrs (non GDM 5.1) 4 20 yrs (72% followed for entire time) yrs (0.8) 5 2.2 yrs (GDM; 8.6 yrs (nonGDM) 6 6.2 yrs (0.8) 7 5 yrs 8 16-24 wks 9 5.7 yrs (GDM 1.0-11.6); 6.1 (nonGDM 1.5-13.1) 10 6.16 yrs (0.05-13.73) 11 1 yr 12 yrs 13 5-11 yrs 14 6 wks 15 7 yrs 16 7.5 yrs 17 4.8 yrs (GDM)/5.5 yrs (nonGDM 18 22-28 yrs 19 3-4 yrs	NA	2,3	

Screening

Screening for Type 2 Diabetes

Problem Formulation 4

Clinical Question:	Is screening for type 2 diabetes recommended?
Population:	All adults aged 18 and older at average or increased risk of type 2 diabetes
Health Intervention:	▪ Screening ▪ No screening
Most Important Health Outcomes:	▪ Prevention or delayed onset of diabetes ▪ Prevention or delayed diabetes complications ▪ Reduction in Morbidity and Mortality from diabetes
Intermediate Outcomes	▪ Complications of diabetes, e.g., macrovascular disease, peripheral vascular disease, cerebrovascular disease, or cardiovascular disease

Test to Screen for Impaired Glucose Control

Problem Formulation 5

Clinical Question:	Which test should be performed to identify people with Impared Glucose Control (IGC)?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals on who, when, and how to delay the onset of diabetes.
Population:	All adults
Health Problem:	Development of type 2 diabetes
Health Intervention:	▪ Lifestyle interventions ▪ Drug therapy intervention ▪ Combination therapy (lifestyle plus medication) ▪ No intervention
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Delayed onset of diabetes ▪ Delayed diabetes complications ▪ Improved functional /health status ▪ Improved quality of life ▪ Decreased mortality ▪ Decreased hospitalization ▪ Decreased office visits
Side Effects of the Intervention:	▪ Quality of Life ▪ Functional health status ▪ GI upset

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH] ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07-09/4/09	1/65
	Diabetes, screening(non-insulin-dependent[All Fields] OR (non[All Fields] AND ("insulin"[MeSH Terms] OR "insulin"[All Fields]) AND dependent[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/08"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Randomized, controlled trial, All Adult: 19+ years English, Human	8/08/07 – 09/08/09	0/0

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	Diabetes, screening (non-insulin-dependent[All Fields] OR (non[All Fields] AND ("insulin"[MeSH Terms] OR "insulin"[All Fields]) AND dependent[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/08"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years English, Human	8/08/07 – 09/08/09	0/3
	Diabetes, detection, screening, diagnosis Diabetes, early detection, diagnosis, screening ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/08"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years English, Human	8/08/07 – 09/08/09	0/18

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	Diabetes, detection, screening, diagnosis ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/08"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	Randomized, controlled trial, All Adult: 19+ years English, Human	8/08/07 – 09/08/09	0/258
	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/08/07	0/117
	"Diabetes Mellitus, Non-Insulin-Dependent/prevention and control"[MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	2001 – 8/08/07	0/102
	((("Diabetes Mellitus, Non-Insulin-Dependent/prevention and control"[MAJR] AND (("glucose intolerance/ complications"[MESH] OR "glucose intolerance/drug therapy"[MESH]) OR "glucose intolerance/therapy"[MESH])	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 09/04/01	0/7
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05-09/4/09	0/67
Clinical Evidence	No terms used - searched book section Endocrine and Metabolic Disorders, Conditions: Diabetes, Pregnancy and Childbirth	Systematic reviews and RCTs	7/15/05-09/4/09	0/0

Pharmacological Management of Diabetes

Blood Pressure Threshold to Initiate Drug Therapy in Patients with Diabetes and Hypertension

Problem Formulation 6

Clinical Question:	Is there a threshold to initiate blood pressure therapy and a target which, when achieved, will prevent the onset/progression of diabetes complications?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes and known hypertension.
Population:	Non-pregnant adults with type 1 and type 2 diabetes and known hypertension who do not have heart failure, renal insufficiency or known coronary heart disease.
Health Problem:	Hypertension in Patients with Diabetes
Health Intervention:	▪ Diastolic and systolic blood pressure thresholds and targets using monotherapy with: beta-blockers, thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, ▪ Combination therapy ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists, registered dieticians, and health educators
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ All-cause mortality ▪ CV mortality ▪ Stroke ▪ Non-fatal myocardial infarction ▪ Heart failure ▪ Combined cardiovascular disease

Side Effects of the Intervention:	▪ Persistent dry cough
	▪ Rash
	▪ Weight gain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Hypotension,
	  ▪ Bradycardia,
	  ▪ Hypoglycemia,
	  ▪ Hypokalemia,
	  ▪ Hyperkalemia

Blood Pressure Threshold to Initiate Combination Drug Therapy in Patients with Diabetes and Hypertension

Problem Formulation 7

Clinical Question:	Is there a threshold to initiate combination blood pressure therapy which, when used, will prevent the onset/progression of diabetes complications?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes and known hypertension.
Population:	Non-pregnant adults with type 1 and type 2 diabetes and known hypertension 20/10 mmHg above goal who do not have heart failure, renal insufficiency, or known coronary heart disease.
Health Problem:	Hypertension in Patients with Diabetes
Health Intervention:	▪ Monotherapy with: beta-blockers, thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers ▪ Combination therapy
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists, registered dieticians, and health educators
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ All-cause mortality ▪ CV mortality ▪ Stroke ▪ Non-fatal myocardial infarction ▪ Heart failure ▪ Combined cardiovascular disease

Side Effects of the Intervention:	▪ Persistent dry cough
	▪ Rash
	▪ Weight gain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Hypotension,
	  ▪ Bradycardia,
	  ▪ Hypoglycemia,
	  ▪ Hypokalemia,
	  ▪ Hyperkalemia

Initial Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease or Microalbuminuria

Problem Formulation 8

Clinical Question:	What class of medication(s) is the most effective first-line therapy for type 1 and 2 diabetes patients with known hypertension?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes and known hypertension.
Population:	Non-pregnant adults with type 1 and type 2 diabetes and known hypertension who do not have heart failure, renal insufficiency or known coronary heart disease.
Health Problem:	Hypertension in Patients with Diabetes
Health Intervention:	▪ Beta-blockers ▪ Thiazide diuretics ▪ Calcium channel blockers ▪ ACE inhibitors ▪ Angiotensin receptor blockers ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ All-cause mortality ▪ CV mortality ▪ Stroke ▪ Non-fatal myocardial infarction ▪ Heart failure ▪ Combined cardiovascular disease

Side Effects of the Intervention:	▪ Persistent dry cough
	▪ Rash
	▪ Weight gain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Hypotension,
	  ▪ Bradycardia,
	  ▪ Hypoglycemia,
	  ▪ Hypokalemia,
	  ▪ Hyperkalemia

Step Therapy in the Treatment of Diabetes and Hypertension in the Absence of Heart Failure or Known Coronary Heart Disease

Problem Formulation 9

Clinical Question:	When patients with diabetes cannot attain sufficient blood pressure control with first-line agents, what is the appropriate next step for therapy?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes and known hypertension.
Population:	Non-pregnant adults with type 1 and type 2 diabetes and known hypertension who do not have heart failure, renal insufficiency or known coronary heart disease.
Health Problem:	Hypertension in Patients with Diabetes
Health Intervention:	▪ Beta-blockers ▪ Thiazide diuretics ▪ Calcium channel blockers ▪ ACE inhibitors ▪ Angiotensin receptor blockers ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ All-cause mortality ▪ CV mortality ▪ Stroke ▪ Non-fatal myocardial infarction ▪ Heart failure ▪ Combined cardiovascular disease

Side Effects of the Intervention:	▪ Persistent dry cough
	▪ Rash
	▪ Weight gain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Hypotension,
	  ▪ Bradycardia,
	  ▪ Hypoglycemia,
	  ▪ Hypokalemia,
	  ▪ Hyperkalemia

Drug Therapy for Patients with Diabetes, Hypertension, and Microalbuminuria or Diabetic Nephropathy

Problem Formulation 10

Clinical Question:	Is it appropriate to substitute an ARB for an ACE inhibitor in patients with hypertension, diabetes, and microalbuminuria?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes and known hypertension.
Population:	Non-pregnant adults with type 1 and type 2 diabetes and known hypertension in whom ACE inhibitors are contraindicated
Health Problem:	Hypertension in Patients with Diabetes
Health Intervention:	▪ Beta-blockers ▪ Thiazide diuretics ▪ Calcium channel blockers ▪ ACE inhibitors ▪ Angiotensin receptor blockers ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ All-cause mortality ▪ CV mortality ▪ Stroke ▪ Non-fatal myocardial infarction ▪ Heart failure ▪ Combined cardiovascular disease

Side Effects of the Intervention:	▪ Persistent dry cough
	▪ Rash
	▪ Weight gain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Hypotension,
	  ▪ Bradycardia,
	  ▪ Hypoglycemia,
	  ▪ Hypokalemia,
	  ▪ Hyperkalemia

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 8/2007	0/113
	(((((("Diabetes Mellitus" [MESH]) AND (hypertension/drug therapy[MESH] OR hypertension/prevention and control[MESH]))AND ((("Angiotensin-Converting Enzyme Inhibitors/therapeutic use"[MESH] OR Hydrochlorothiazide/therapeutic use[MESH]) OR "Adrenergic beta-Antagonists/therapeutic use"[MESH]) OR "calcium channel blockers/therapeutic use"[MESH]))	Randomized, controlled trial, All Adult: 19+ years English, Human	2000 – 08/2007	1/277
PubMed	"Hypertension"[MeSH Terms] AND "stepped-care"[Text Word]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/15/05	0/2
		Randomized, controlled trial, Adult, English, Human	1965 – 7/15/05	0/36
PubMed	("Hypertension"[MESH] AND (((((((("Adrenergic beta-Antagonists"[MESH] OR "angiotensin-converting enzyme inhibitors"[MESH]) OR "Adrenergic alpha-Antagonists"[MESH]) OR "calcium channel blockers"[MESH]) OR "Diuretics"[All Fields])	Randomized, controlled trial, All Adult: 19+ years English, Human	1/2001 – 3/2003	2/239
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Evidence Tables

Table 10.1: Summary of New Evidence - 2005 Search

Study	Inclusion & Exclusion Criteria	Age	Limitations / biases	Intervention & dose – N and Final N	Duration	Outcome	Relative Risk (RR) or Hazard Ratio(HR) 95% CI	NNT	p value
ARB vs. CCB									
Berl (2003) RCT	Adults with type 2 diabetic nephropathy and HTN	30-70	Limited power to detect important differences between groups in mortality or strokes; most patients received several antihypertensive agents.	I. irbesartan (300 mg/d) - 579 II amlodopine (10 mg/d) – 567 III. placebo- 569 N=1715 Final N-=1704	2.6 yrs median	<u>Cardiovascular Composite</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine <u>Cardiovascular Death</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine <u>Congestive Heart Failure</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine <u>Myocardial Infarction</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine <u>Cerebrovascular Accident</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine <u>Cardiac Revascularization</u> Irbesartan vs. placebo Amlodopine vs. placebo Irbesartan vs. amlodopine	 0.90 (0.74–1.10) 1.00 (0.83–1.21) 0.90 (0.74–1.10) 1.08 (0.72–1.60) 0.79 (0.51–1.22) 1.36 (0.89–2.07) 0.72 (0.52–1.00) 1.11 (0.83–1.50) 0.65 (0.48–0.87) 0.90 (0.60–1.33) 0.58 (0.37–0.92) 1.54 (0.97–2.45) 1.01 (0.61–1.67) 0.65 (0.35–1.22) 1.55 (0.84–2.87) 0.80 (0.49–1.30) 0.86 (0.54–1.38) 0.93 (0.55–1.55)	 - - - - - - 43.6 - 16.7 - - - - - - - - -	 NS NS NS NS NS NS 0.048 NS 0.004 NS .021 NS NS NS NS NS NS NS

Study	Inclusion & Exclusion Criteria	Age	Limitations / biases	Intervention & dose – N and Final N	Duration	Outcome	Relative Risk (RR) or Hazard Ratio(HR) 95% CI	NNT	p value
Table 10.2CCB vs. ACE vs. Diuretic									
Whelton (2005) RCT	Adults with diabetes and HTN plus one other risk factor for CHD	55+	Diabetes subgroup not randomized	I. chlorthalidone (12.5-25 mg/d) II. amlodopine (2.5-10 mg/d) III. lisinopril (10-40 mg/d) N=13,101 (DM subgroup) 25% dropout	4.9 yr mean	<u>CHD</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>All Cause Mortality</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>Combined CHD</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>Stroke</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>Heart Failure</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>Combined CVD</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone <u>ESRD</u> Amlodopine vs. chlorthalidone Lisinopril vs. chlorthalidone	 0.97 (0.86-1.10) 0.97 (0.85-1.10) 0.95 (0.86-1.05) 0.99 (0.89-1.09) 1.02 (0.93-1.12) 1.03 (0.94-1.13) 0.89 (0.74-1.06) 1.06 (0.89-1.26) 1.39 (1.22-1.59) 1.15 (1.00-1.32) 1.06 (0.98-1.14) 1.07 (0.99-1.15) 1.27 (0.97-1.67) 1.09 (0.82-1.46)	 - - - - - - 5 - - - - -	 NS NS NS NS NS NS <.001 NS NS NS NS NS

Study	Inclusion & Exclusion Criteria	Age	Limitations / biases	Intervention & dose – N and Final N	Duration	Outcome	Relative Risk (RR) or Hazard Ratio(HR) 95% CI	NNT	p value
CCB vs. BB									
Bakris (2004) RCT	Adults with HTN and documented CAD	>50	Diabetes subgroup not randomized. Diabetes not confirmed by lab testing	I. verapamil (240 mg/d and titrated to max dose for BP<130/85)-3169 II. atenolol (50 mg/d and titrated to max dose for BP<130/85)-3231 N=6400 (DM subgrp)	2.7 yrs mean	Primary Outcome Event (first occurrence of all cause death, non fatal MI, or nonfatal stroke) Death Nonfatal MI Nonfatal stroke Cardiovascular death Cardiovascular hospitalization	1.05(0.92-1.19) 1.06(0.92-1.23) 1.04 (0.74-1.47) 0.84(0.56-1.24) 1.20(0.97-1.48) 0.91(0.77-1.07)	- - - - - -	NS NS NS NS NS NS
CCB vs. Diuretics or BB									
Black (2003) RCT	HTN plus one other risk factor (e.g., diabetes or smoker)	>=55	Diabetes group not randomized. Study terminated prematurely for commercial reasons. 7% lost to f/up	I. COER verapamil (180 mg)-8241 II. atenolol(50 mg) or HCTZ (12.5 mg)-8361 N=3239 (DM subgrp)	3 yrs mean	MI, stroke or CV death	0.86 (0.66-1.12)	-	NS
Mancia (2003) RCT	HTN plus one additional risk factor	55-80	Diabetes group not randomized. Insufficient events in the DM subgroup to make comparison of primary end point	I. Nifedpine (30 mg/d)-649 II. Co-amilozide (25mg HCTZ and 2.5 amiloride)-653 N=1302 (DM subgrp)	4 yrs mean	CV death, MI, heart failure, or stroke	0.99 (0.69-1.40)	-	NS
Diuretic vs. Placebo									
Kostis (2005) RCT	HTN	>=60	Retrospective review. No information on non fatal endpoints, pharmacologic therapy, and BP after the end of the double-blind phase.	I. Chlorthalidone (12.5-250 mg/d) II. Placebo N=1226 (DM subgrp)	14.3 mean	CV mortality Total mortality	0.69 (0.53-0.85) 0.81 (0.68-0.95)	- -	<.05 <.05

Table 10.4: ACE Inhibitors vs. Diuretics for Initial Treatment of Hypertension in Diabetes *RCT*

Study, Total n	Treatment Groups Size and Drug	Study Population	Results			Comments
ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981-97. (RCT) Mean Follow-up – 4.9 years	Goal BP achieved by titrating the assigned study drug (step 1) and adding open label agents (step 2or 3) when necessary Step 1 drug treatments (Diabetes subgroup, n= 12,063) Chlorthalidone (diuretic) n = 5528 25 mg daily Amlodipine (CCB) n = 3323 2.5, 5, 19 mg daily Lisinopril (ACE-I) n= 3212 10, 20, 40 mg daily Step 2 drugs (open label): Atenolol (25-100 mg daily) Clonidine (0.1-0.3 mg daily) Reserpine(0.05-0.2 mg daily) Step 3 drug (open label): Hydralazine(25-100 mg bid) Other drugs, including low doses of open-label step 1 drug classes, were allowed if indicated.	Patient eligibility criteria: Men and women ≥ 55 years of age SBP ≥ 140 mmHg and/or DBP > 90 mmHg (or took hypertension medication) ≥1 additional risk factor for CHD, including: previous MI or stroke, LVH by electro- or echocardiogram, type 2 diabetes, current cigarette smoking, low HDL cholesterol Baseline Characteristics: 36% Diabetic 67 years old (mean) 47% women 35% black/African American 19% Hispanic	ACEI vs. Diuretic--Diabetes Subgroup Primary outcome(Non fatal MI and Fatal CHD) All-cause mortality Combined CHD (CHD death, nonfatal MI, coronary revascularization, hospitalized angina) Stroke Combined CVD events(CHD death, nonfatal MI, stroke, coronary revascularization, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease) Heart Failure CCB vs. Diuretic- Diabetes Subgroup Primary outcome, (Non fatal MI and Fatal CHD) ll-cause mortality Combined CHD (CHD death, nonfatal MI, coronary revascularization, hospitalized angina) Stroke Combined CVD events(CHD death, nonfatal MI, stroke, coronary revascularization, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease) Heart Failure *statistically significant	RR (95%CI) 1.00 (0.87-1.14) 1.02 (0.91-1.13) 1.03 (0.93-1.15) 1.07 (0.90-1.28) 1.08 (1.00-1.17) 1.22 (1.05-1.42)* 0.99 (0.87-1.13) 0.96 (0.87-1.07) 1.04 (0.94-1.14) 0.90 (0.75-1.08) 1.06 (0.98-1.15) 1.42 (1.23-1.64)*	p ns ns ns ns ns ns ns ns ns ns	Significant results: Diuretics reduce the risk of all heart failure (and serious heart failure alone) over CCBs and ACE-I in the diabetes subgroup Bias: Newer agents (e.g., ARBs, selective aldosterone antagonists)were not evaluated Equivalent BP goals were not achieved in the treatment groups Because diuretics, ACE, CCBs, and alpha-blockers were evaluated, the agents available for step-up led to an artificial regimen (sympatholytics rather than diuretics and CCBs) of step up drugs in the ACE-I group. This may have contributed to higher BPs in the ACE group esp. in the black/African American subgroup.

Table 10.5: ARBs vs. Beta-Blockers for Initial Treatment of Hypertension in Diabetes *RCT*

Study, Total n	Treatment Groups Size and Drug	Study Population	Results			Comments
Lindholm. L. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359:1004-10. Randomized, controlled trial n= 1195 945 centers	**Study Design:** Randomized, double-masked, double-dummy, parallel-group, multicenter clinical trial, with at least four-year follow-up. Intention-to-treat analysis Treatment Groups: Selective angiotensin-II type 1-receptor antagonist (Losartan) or ARB + diuretic n=586 Beta-blocker (atenolol) or BB + diuretic n= 609 Patients initially received losartan 50 mg or atenolol 50 mg. After 2 months, hydrochlorothiazide (HCTZ) 12.5 mg was added if blood pressure was not at, or below, goal blood pressure. After 4 months, the dose of losartan or atenolol was doubled to 100 mg plus HCTZ 12.5 mg if blood pressure was still inadequately controlled. At month 6, additional open-label antihypertensive medication, including upward titration of HCTZ, was added in order to reach goal blood pressure.	Patients aged 55-80 yrs with essential hypertension (sitting BP 160-200/95-155 mmHg) and left ventricular hypertrophy (LVH) ascertained by ECG.	**ARB vs. BB- Diabetes Subgroup**	HR (95%CI)	p	*Significant results:* ARB is better than BB at preventing the primary endpoint (CV mortality, stroke, and MI) ARB is better than BB at preventing CV mortality ARB is better than BB at preventing total mortality ARB is better than BB at preventing admittance to hospital for heart failure. Bias: This trial was conducted in a high-risk population – those with evidence of left ventricular hypertrophy. Results may not be applicable to a group without LVH.
			Primary composite endpoint (CV mortality, stroke, and myocardial infarction)	0.76 (0.58-0.98)*	0.031	
			CV mortality	0.63 (0.42-0.95)*	0.028	
			Stroke	0.79 (0.55-1.14)	0.204	
			Myocardial infarction	0.83(0.55-1.25)	0.373	
			Total mortality	0.61 (0.45-0.84)*	0.002	
			Admitted to hospital for angina pectoris	1.06 (0.64-1.76)	0.828	
			Admitted to hospital for heart failure	0.59 (0.38-0.92)*	0.019	
			Revascularization	0.90 (0.64-1.26)	0.533	
			*statistically significant			

Table 10.6: Effect of Antihypertensive Agents vs. Placebo on the Primary Prevention of Cardiovascular Disease in Type 1 and 2 Diabetes *Meta-Analysis*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 [33] **References of studies included in systematic review:** Fuller J, et al. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes mellitus. Cochrane Database Syst Revs. 2000 Curb D, et al. Effect of Diuretic-Based Antihypertensive Treatment on Cardiovascular Disease Risk in Older Patient with diabetes Patients with Isolated Systolic Hypertension. JAMA 1996; 276:1886-1892[137]; Prevention of stroke by antihypertensive drug treatment in older isolated systolic hypertension. Final results of the Systolic Hypertension in the Older adults Program (SHEP). SHEP Cooperative Research Group. JAMA 1991; 265: 3255-64 [28] Tuomilehto J, et al. Effects of Calcium-Channel Blockade in Older Patients with diabetes and Systolic Hypertension. N Engl J Med 1999;340(9):677-684 [14]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 Systematic Review (including 1 RCT) and 1 subsequent RCT **Intervention:** SHEP (chlorthalidone vs. placebo) Syst-Eur (nitredipine vs. placebo) **Settings:** SHEP: US Syst-Eur: Finland **Sample size range:** SHEP: 583 patients with diabetes Syst-Eur: 4695 (495 with diabetes) **Duration of Trials:** SHEP 5 years Syst-Eur: 2 years	**Inclusion criteria:** SHEP: isolated systolic hypertension defined as systolic blood pressure ≥160mmHg and diastolic blood pressure <90mmHg measured on 2 visits (12% of the population were patients with diabetes) Syst-Eur: blood pressure ≥165-219/<95 mmHg while seated, ≥140/<95 mmHg while standing **Age Range:** SHEP: >60 Syst-Eur: ≥60	**Major CV event (fatal or non fatal MI, sudden cardiac death, rapid cardiac death, CABG, angioplasty, fatal or nonfatal stroke, transient ischemic attack, aneurysm, and end-arterectomy)** placebo 83/300 (27.7%) chlorthalidone 57/283 (20.1%) RR 0.66 (0.46, 0.94) NNT 13 **All cause mortality:** placebo 48/300 (16%) chlorthalidone 39/283 (13.8%) RR 0.74 (0.46, 1.18) **Primary prevention of all CV events (MI, CHF, or sudden cardiac death):** placebo 31/240 (12.9%) nitredipine 13/252 (5.2%) ARR 8% (3, 10) RR 0.4 (0.21, 0.75) NNT 13 (10, 13) **Overall Mortality:** placebo 26/240 nitredipine 16/252 ARR +4.5% (-0.7, 7.4) RR 0.96 (0.32, 1.06)	No class of medication had significant adverse effects on metabolism or quality of life at the doses used in the trials.	Systematic reviews of RCTs have found that diuretics and ACE inhibitor reduce CV events in people with diabetes and no previous CV events.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.7: Effect of Antihypertensive Agents vs. Placebo on the Primary and Secondary Prevention of Cardiovascular Disease in Type 1 and 2 Diabetes *Meta-Analysis*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 [33] **References of studies included in systematic review:** Lievre M, et al. Efficacy of diuretics and beta-blockers in patient with diabetes hypertensive patients. Results from a meta-analysis. The INDANA Steering Committee. Diabetes Care 2000;23(Suppl 2):B65-71[138]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 systematic review (4 RCTs) **Intervention:** 1008 on diuretics **Settings:** multicenter **Sample size range:** 15843 (1100 people with diabetes) **Duration of Trials:** 2.2-4.8 years	**Inclusion criteria:** Not stated **Age Range:** >55	**Risk of major CVD events (fatal or non-fatal coronary events or stroke, sudden death, or death from embolism):** diuretics 151/1000 RR 0.8 in favor of diuretics NNT 26	No class of medication had significant adverse effects on metabolism or quality of life at the doses used in the trials.	Systematic reviews of RCTs have found that diuretics reduce CV events in people with diabetes and no previous CV events.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.8: Effect of Antihypertensive Agents vs. Placebo on the Secondary Prevention of Cardiovascular Disease in Type 1 and 2 Diabetes *Meta-Analysis*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 [33] **References of studies included in systematic review:** Fuller J, Stevens LK, Chaturvedi N, Holloway JF. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes mellitus. Cochrane Database Syst Revs. 2000[31]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 systematic review (7 RCTs) **Intervention:** ACE inhibitor vs. placebo beta-blockers vs. placebo **Settings:** Not stated **Sample size range:** Not stated **Duration of Trials:** ≥1 year	**Inclusion criteria:** 2564 people with diabetes **Age Range:** Not stated	**Overall mortality (6 RCTs; 2402 people):** OR 0.82 (0.69, 0.99) in favor of active treatment **CV morbidity plus mortality in long-term secondary prevention (2 RCTs, 654 people):** Placebo 157/338 (46%) Intervention 130/360 (41%) OR 0.82 (0.60, 1.13) NNT 19 (NS) **CVD mortality and morbidity in short-term secondary prevention (533 people):** Placebo 21/288 (7.3%) Intervention 8/245 (3.3%) NNT 25 (17, 1145)	No class of medication had significant adverse effects on metabolism or quality of life at the doses used in the trials.	The results of pooled data from various studies using either ACE inhibitor or beta-blockers show prevention of cardiovascular events in patients with type 2 diabetes who had experienced a prior CV event.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.9: ACE Inhibitors vs. CCB for Initial Treatment of Hypertension in Type 2 Diabetes *Meta-Analysis*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 (33) **References of studies included in systematic review:** Pahor M, et al. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 2000;23:888-892(34) Estacio RO, et al. The effect of nisoldipine as compared with enalapril on cardiovascular events in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52 (36) Tatti P, et al. Outcome results of the Fosfinopril vs. Amlodipine Cardiovascular Events randomised Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998; 21: 597-603(37) Lindholm LH, Comparison of antihypertensive treatment in preventing cardiovascular events in older adult patients with diabetes patients: results from the Swedish trial in old patients with hypertension–2. J Hypertens 2000;18:1671-1675(35)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 systematic review (2 RCTs) and 1 additional RCT **Interventions:** enalapril vs. nisoldipine fosinopril (20 mg/day) vs. amlodipine (10 mg/day) ACE inhibitors vs. calcium antagonists (drugs not specified) vs. conventional treatment (b-blocker or hydrochlorothiazide plus amiloride) **Settings:** US, Italy, and Sweden **Sample size range:** 470 patients with hypertension, 480 without hypertension 380 hypertensive patient with diabetes 6614 older adults patients (719 with diabetes) **Duration of Trials:** 5.6 years 3.5 years 4 years	**Inclusion criteria:** NIDDM, diastolic blood pressure =80mmHG, on no hypertension medication (about 50% had CVD), with no MI 6 months prior to study, and no coronary bypass surgery 3 months prior to study, no serum creatinine concentration greater than 3 mg per deciliter (265 micromol per liter) Diagnosis of NIDDM and hypertension (systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg), no CHD or stroke, no serum creatinine >1.5 mg/dl, no albuminuria >40 micro g/min, no use of other anti-hypertension drugs People with hypertension (subgroup analysis of people with type 2 diabetes) **Age Range:** 40-74 years mean age around 63 older adults patients age 70-84 (mean age 75.8 years)	**Cardiovascular events (enalapril and fosinopril):** calcium channel blockers 151/526 (16%) ACE inhibitors 34/424 (8%) ARR 8% (4, 13) RR 0.49 (0.33, 0.72) NNT 13 (7, 25) **Death, AMI, and stroke (enalapril and fosinopril):** Greater reduction with ACE inhibitors, but not statistically significant **Serum creatinine (fosinopril):** Did not vary significantly between groups during follow-up **Incidence of major cardiovascular events over 4 years :** calcium antagonists 67.7/1000 person years ACE inhibitors 64.2/1000 person years conventional therapy 75.0/1000 person years p=ns between groups **AMI:** calcium antagonists 32/231 (13.9%) ACE inhibitors 17/235 (7.2%) RR 0.51 (0.28, 0.92) p=0.025	In one open-label RCT, people who developed nephropathy were switched to the ACE inhibitor group by their doctor Significantly more patients discontinued taking nisoldipine than enalapril due to headaches (p=0.009) Significantly more patients discontinued taking enalapril than nisoldipine because of malaise or fatigue (p=0.005)	There is clear evidence that ACE inhibitors are superior to calcium channel blockers as initial therapy for hypertension.

Table 10.10: ACE Inhibitors vs. Diuretics vs. Beta-Blockers (plus Diuretics if necessary) for Initial Treatment of Hypertension in Diabetes (CAPPP) *Summary of a Meta-Analysis from Clinical Evidence*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96[33] **References of studies included in systematic review:** Pahor M, et al. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 2000;23:888-892[34] Hansson L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999; 353:611-616[38]; Subgroup analysis: Niskanene L, et al. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/b-blocker-based treatment regimen: a subanalysis of the captopril prevention project. Diabetes Care 2001;24(12):2091-2096[139]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 systematic review (1 RCTs) **Interventions:** 50 mg captopril (dose could be increased to 100 mg daily and a diuretic could be added if necessary; calcium channel blocker could be added as a last step) vs. Conventional therapy (50-100 mg/day atenolol or metoprolol, plus 25 mg/day hydrochlorothiazide or 2.5 mg/day bendrofluazide; calcium channel blocker could be added as last step) Note: Treatment goal was diastolic blood pressure ≤90 mmHg **Settings:** Sweden **Sample size:** 10,985 patients (572 patient with diabetes) **Duration of Trials:** 6.1 years	**Inclusion criteria:** Age 25-66 with treated or untreated hypertension (diastolic bp ≥100mmHg on two separate occasions) who did not have secondary hypertension , nor a serum creatinine concentration >150micro mol/L (subgroup analysis of people with diabetes) **Mean Age:** about 55	**AMI, stroke, or death:** conventional therapy 46/263 (17%) captopril 35/309 (11%) RR 0.59 (0.38, 0.91); p=0.018 **Fatal and non-fatal MI:** conventional therapy 27/263 (10%) captopril 12/309 (4%) RR 0.34 (0.17, 0.67); p=0.002 **Fatal and non-fatal stroke:** conventional therapy 19/263 (7%) captopril 23/309 (7%) RR 1.02 (0.55, 1.88); p=0.96 **All fatal events:** conventional therapy not stated captopril not stated RR 0.67 (0.46, 0.96); p=0.030	None noted	There is no clear evidence comparing ACE inhibitors directly to diuretics. ACE inhibitors were superior to conventional therapy in preventing AMI, stroke and death.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.11: ACE Inhibitors vs. Beta-Blockers for Initial Treatment of Hypertension in Type 2 Diabetes (UKPDS 39) *Summary of a Meta-Analysis from Clinical Evidence*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96[33] **References of studies included in systematic review:** Pahor M, et al. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 2000;23:888-892[34] Efficacy of atenolol and captopril in reducing risk of macrovasular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-719[39]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 1 RCT **Interventions:** captopril vs. atenolol **Settings:** UK **Sample size range:** 758 with diabetes **Duration of Trials:** 8.4 years	**Inclusion criteria:** Hypertensive patients (mean bp 160/94 mmHg) with type 2 diabetes **Baseline characteristics:** 55% men, 56 patients in the captopril group had urinary albumin ≥50 mg/l and 8 had urinary albumin ≥300 mg/l; 58 patients in the captopril group had urinary albumin ≥50 mg/l and 10 had urinary albumin ≥300 mg/l **Age Range:** mean age 56	**Cardiovascular events** captopril 102/400 (25.5%) atenolol 75/358 (20.9%) ARI +5% (-1, 11) RR 1.22 (0.94, 1.58) **Urinary albumin concentration ≥50 mg/l:** captopril 48/153 (31%) atenolol 38/146 (26%) p=0.31 **Clinical proteinuria ≥300 mg/l:** captopril 7/153 (5%) atenolol 14/146 (10%) p=0.090	**Weight Gain:** captopril 1.6 kg atenolol 3.4 kg p=0.02 **Mean HbA1c over first 4 years:** captopril 7.0% atenolol 7.5% p=0.004 There was no difference between atenolol and captopril in rates of hypoglycemia, lipid concentrations, tolerability, blood pressure lowering, or prevention of disease events	Both ACE and beta-blocker prevent CVD. There is no clear evidence whether ACE inhibitor is superior to beta-blockers in prevention of cardiovascular disease. There is a trend in reducing albuminuria favoring captopril, however the numbers are too small to be meaningful.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.12: ACE Inhibitor vs. Angiotensin II Blockers in Patients with Type 1 Diabetes, Hypertension, and Nephropathy *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Safety	Bias
Andersen S, et al. Renoprotective Effects of Angiotensin II Receptor Blockade in Type 1 Patient with diabetes Patients with Patient with diabetes Nephropathy. Kidney Int. Feb 2000;57(2):601-6[50] Location: Denmark Sponsor: grant from Merck, Sharp & Dohme	Type of study: RCT Blinding: double-blind Cross-over Follow-up: Duration: 5 periods, each lasting 2 months (10 months)	Inclusion criteria: Type 1 diabetes, patient with diabetic nephropathy (persistent albuminuria >300 mg/24hours), GFR> 60mL/min/1.73m^2, Office bp>145/85mmHg, Age 18-70 years Exclusion criteria: History of malignant hypertension, CHF, MI, or stroke within 3 months prior to the study period, patients who forgot to take the study medication more than once a week Baseline data: 10 men, 6 women, mean age 42±2, mean duration of diabetes 33±2, mean albuminuria mg/24 hours 1156 (643, 2080), mean blood pressure 147/82, hypertensive medications were withdrawn for at least 4 weeks prior to start of study.	Groups: C: placebo Rx1: losartan 50 mg Rx2: losartan 100 mg Rx3: enalapril 10 mg Rx4 enalapril 20 mg	Initial N: 16 Final N: 16 Compliance: Not stated	HbA_{1c} (%): C: 8.8±0.3 Rx1: 9.0±0.4 Rx2: 9.2±0.3 Rx3: 8.8±0.4 Rx4 8.9±0.3 p not state Urinary albumin mg/24h (Geometric Mean): C: 1156 (643, 2080) Rx1: 775 (445, 1349) Rx2: 651 (377, 1126) Rx3: 631 (340, 1173) Rx4 477 (251, 910) p< 0.05 for each treatment group vs. placebo p not reported for drug-drug comparisons Serum creatinine (µmol/l): C: 96±5 Rx1: 94±5 Rx2: 92±7 Rx3: 96±5 Rx4 89±6 p=ns for all comparisons	5 patients received furosemide during treatment periods to prevent peripheral edema No patients reported side-effects that could be related to study medication Urinary sodium excretions were elevated above normal level (150 mmol/24h) during all 5 treatment periods Cholesterol, creatinine, and serum sodium remained unchanged	Small n Short follow-up period

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.13: Placebo vs. Angiotensin II Blockers in Patients with Type 2 Diabetes, Hypertension, and Nephropathy (RENAAL) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Brenner BM, et al. **Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.** N Engl J Med 2001; 345(12):861-869[48] Brenner BM, et al. The losartan renal protection study-rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan). JRAAS. 2000;1(4):328-335[140] **Location:** multicenter **Sponsor:** Merck	**Type of study:** RCT **Blinding:** triple-blind **Follow-up:** 3.4 years (stopped early due to beneficial effect of therapy)	**Inclusion criteria:** diagnosis of type 2 diabetes, age 31-70, urinary albumin:creatinine ratio of at least 300 mg/g, serum creatinine between 1.5-3.0 mg/dl, with or with out hypertension **Exclusion criteria:** type 1 diabetes, patient with diabetes renal disease, history of MI or CABG within one month prior to study, cerebral vascular accident or percutaneous transluminal coronary angioplasty within six months prior to study, history of HF, patients were not allowed to remain on medications that block angiotensin production or action **Baseline data:** 956 men, 557 women, mean age 60±7, 48.6% Caucasian, 15.2% black/African American, 16.7% Asian, 18.2% Hispanic, average albumin:creatnine ratio1867 mg/g, average serum creatinine level 1.9 mg/dl, mean blood pressure 153/82 mmHg	**Groups:** C: placebo Rx: losartan 50 mg/day (dose increased to 100 mg/day if target blood pressure of 140/90 mmHg was not achieved; other anti-hypertension medications were added if target bp was not achieved via 100 mg/day)	**Initial N:** C: 762 Rx: 751 **Final N:** Not stated	**Composite of the time to first event of doubling of serum creatinine, ESRD, or death:** C: 359 (47.1%) Rx: 327 (43.5%) Risk Reduction (RR) 16% (2, 28); p=0.02 Effects largely independent of achieved bp **Progression to ESRD (requiring dialysis or kidney transplantation):** C: 194 (25.5%) Rx: 147 (19.6%) RR 28%(11, 42); p=0.002 **Doubling of serum creatinine:** C: 198 (26%) Rx: 162 (21.6%) RR 25% (8, 39); p=0.006 **Death:** C: 155 (20.3%) Rx: 158 (21%) RR –2% (-27, 19)p=0.88 **Hospitalization for HF:** C: 16.7% Rx: 11.9 32% Risk Reduction; p=0.005 **Discontinuation of Study Therapy due to Adverse Events:** C: 21.7% Rx: 17.2% p not stated	none noted

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.14: Placebo vs. Angiotensin II Blockers in Patients with Type 2 Diabetes, Hypertension, and Nephropathy (IRMA-II) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Parving HH, et al. **The effect of irbesartan on the development of patient with diabetes nephropathy in patients with type 2 diabetes.** N Engl J Med 2001;345(12):870-878[49] **Location:** 96 centers worldwide **Sponsor:** Supported by a grant from Bristol Myers Squibb and Sanofi-Synthelabo	**Type of study:** RCT Multicenter study **Blinding:** double-blind **Follow-up:** 2 years	**Inclusion criteria:** Age 30-70, type 2 diabetes (WHO criteria), persistent microalbuminuria (albumin excretion rate 20-200mcg/liter) and a serum creatinine concentration of ≤1.5 mg/dl in men and 1.1 mg/dl in women, hypertension (bp >135/85) **Exclusion criteria:** patient with diabetes kidney disease, cancer, life-threatening disease with death expected to occur within two years, and indication for ACE inhibitor or ARB **Baseline data:** 404 men, 186 women, mean age about 58 years	**Groups:** C: placebo Rx1: irbesartan 150 mg/daily Rx2: irbesartan 300 mg/daily	**Initial N:** 590 C: 201 Rx1: 195 Rx2: 194 **Final N:** C: 171 (85%) Rx1: 168 (86%) Rx2: 172 (89%)	**Nephropathy (urinary albumin excretion rate >200mcg per minute and at least 30% higher than baseline on at least 2 consecutive visits):** C: 30 (14.9%) Rx1: 19 (9.7%) Rx2: 10 (5.2%) C vs. Rx1 p=0.08 C vs. Rx2 p<0.001 Rx1 vs. Rx2 p=not stated Unadjusted Hazard ratio (HR) for Rx1 0.61 (0.34, 1.08); p=0.08 Unadjusted HR for Rx2 0.30 (0.14, 0.61); p<0.001 Adjusted HR for Rx1 0.56 (0.21, 0.99); p=0.05 Adjusted HR for Rx2 0.32 (0.15, 0.65); p<0.001 **Nonfatal CV events:** C: 8.7% Rx1: not stated Rx2: 4.5% C vs. Rx2 p<0.11 **Adverse Events:** C: 22.8% Rx1 + Rx2: 15.4% P=0.02	small N

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.15: Calcium Channel Blocker vs. Angiotensin II Blockers in Patients with Type 2 Diabetes, Hypertension, and Nephropathy (IDNT) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Lewis EJ, et al. **Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.** N Engl J Med 2001;345(12):851-860[52] Rodby RA, et al. The Irbesartan Type II Patient with diabetes Nephropathy Trial: study design and baseline patient characteristics. Nephrol Dial Transplant 2000;15:487-97[53] **Location:** 225 Clinics worldwide **Sponsor:** Supported by a grant from Bristol Myers Squibb and Sanofi-Synthelabo	**Type of study:** RCT Multicenter study **Blinding:** double-blind **Follow-up:** 2.6 years	**Inclusion criteria:** Age 30-70 (patients <30 included if biopsy-confirmed patient with diabetes nephropathy present), clinical history of type 2 diabetes (hyperglycemia requiring insulin with >1 yr period between time of diagnosis and insulin usage or with elevated fasting or stimulated C-peptide or hyperglycemia not requiring insulin), patient with diabetic nephropathy (≥900 mg 24-hr urine protein excretion or serum creatinine between 1.0-3.0 mg/dl in women and 1.2-3.0 mg/dl in men), HTN defined as seated bp >135/85 if untreated or receiving antihypertensive meds **Exclusion criteria:** Age of onset of type 2 DM <20 yrs, type 1 DM, absolute requirement for ACE-I, AIIRA or CCB, CV diagnosis within 3 mo of study entry (unstable angina, MI, CABG or PTCA within 3 mo of study entry, NYHA class III or IV heart failure, TIA within 6 mo of study entry, or stroke), serum potassium outside normal range **Baseline data:** 1140 men, 575 women, (more women in the placebo group; p=0.02) age 59±8 years, duration of diabetes 15±9 years, height 168±11 cm (5 ft 6 in), weight 87±19 kg (192 lb), body mass index 31±7 kg/m^2, blood pressure 156+/-18 mmHg/85±11 mmHg, serum creatinine 150±53 micromol/l (1.7±0.6 mg/dl), creatinine clearance 66±34 ml/min and 24 h urine protein 4.0±3.5 g/day	**Groups:** C: placebo Rx1: irbesartan 75-300 mg/daily (75 mg PO QD, titrate up by doubling dose Q2wk to maximum of 300 mg) Rx2: amlodipine 2.5-10 mg/daily (2.5 mg PO QD, titrate up by doubling dose Q2wk to max of 10 mg) Other antihypertensive agents added PRN for bp control (<135/85) EXCEPT ACE-Is, AIIRAs, and CCBs	**Initial N:** 1715 C: 569 Rx1: 579 Rx2: 567 **Compliance:** 11% lost to follow-up	**Doubling serum creatinine, ESRD, or death:** C: 222 (39%) Rx1: 189 (32.6%) Rx2: 233 (41.1%) C vs. Rx1 RR 0.81 (0.67, 0.99); p=0.03 C vs. Rx2 RR 1.07 (0.89, 1.29); p=0.47 Rx1 vs. Rx2 RR 0.76 (0.63, 0.92); p=0.005 **ESRD:** C: 101 (17.8%) Rx1: 82 (14.2%) Rx2: 104 (18.3%) C vs. Rx1 RR 0.83 (0.62, 1.11); p=0.19 C vs. Rx2 RR 1.09 (0.82, 1.43); p=0.56 Rx1 vs. Rx2 RR 0.76 (0.57, 1.02); p=0.06 **Doubling of serum creatinine:** C: 135 (23.7%) Rx1: 98 (16.9%) Rx2: 144 (25.4%) C vs. Rx1 RR 0.71 (0.54, 0.92); p=0.009 C vs. Rx2 RR 1.15 (0.91, 1.46); p=0.24 Rx1 vs. Rx2 RR 0.61 (0.48, 0.79); p<0.001 **Death:** C: 93 (16.3%) Rx1: 87 (15%) Rx2: 83 (14.6%) C vs. Rx1 RR 0.94 (0.70, 1.27); p=0.69 C vs. Rx2 RR 0.90 (0.66, 1.21); p=0.47 Rx1 vs. Rx2 RR 1.05 (0.78, 1.42); p=0.75	none noted

Table 10.16: ACE Inhibitor vs. ARB for Type 1 and 2 Diabetes, Hypertension, and Nephropathy (CALM) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Mogensen, CE, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000; 321:1440-1444 (51) Location: Multicenter Sponsor: AstraZeneca	Type of study: RCT Blinding: Double Blind Follow-up: 24 weeks	Inclusion criteria: type 2 diabetes, age 30-75, diagnosed with hypertension (diastolic bp 90-110 mmHg), and microalbuminuria (albumin:creatinine ratio 2.5-25 mg/mmol) Exclusion criteria: BMI ≥ 40 kg/m2, systolic blood pressure >200 mmHg, non-diabetic cause of secondary hypertension, cardiovascular event in the past six months, serum creatinine concentration ≥ 130 ×6d mol/l in women and ≥ 150 ×6d mol/l in men, serum potassium concentration >5.5 mmol/l, glycated haemoglobin concentration (HbA1c) >10%, pregnancy or potential pregnancy, and breast feeding. Baseline data: mean age about 60, 128 men, 69 women, mean systolic bp about 162 mmHg, mean diastolic bp about 60 mmHg, mean albumin:creatinine ration 5.9-6.6 mg/mmol	Groups: Rx1 16 mg/day candesartan Rx2 20 mg/day lisinopril Rx3 candesartan or for 12 weeks then candesartan plus lisinopril	Initial N: Rx1 66 Rx2 64 Rx3 69 Final N: Rx1 66 Rx2 64 Rx3 67 Compliance: Not stated	Adjusted mean urinary albumin:creatinine ratio: Rx1 24% (0, 43) Rx2 39% (20, 54) Rx3 50% (36, 61) Rx1 vs. Rx3 34% (3, 55); p=0.04 Rx2 vs. Rx3 18% (-20, 44); p>0.20	Small n Short follow-up

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 10.17: Effects of ACE Inhibitor on Mixed Primary and Secondary Prevention of CV Outcomes in People with Diabetes (HOPE study) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE and MICR-HOPE substudy. Lancet. 2000;355:253-59[32] Location: 19 countries in N & S America and Europe (Argentina, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, Netherlands, Norway, Spain, Switzerland, U.K., and U.S.A.) Sponsor: Funding from Medical Research Council of Canada; Hoecst-Marion Roussel; AstraZeneca; King Pharmaceuticals; Natural Source Vitamin E Association; NEGMA and the heart and Stroke Foundation of Ontario	Type of study: RCT Blinding: Originally blinded, then changed to open label at 4 years Follow-up: 4.5 years (stopped 6 months early due to efficacy)	Inclusion criteria: With or without diabetes; age 55 years or older; history of cardiovascular disease (CAD, stroke, or PVD) or diabetes plus at least one other CV risk factor (Tchol >5.2 mmol/l, HDL <=0.9 mmol/l, hypertension, known microalbuminuria, or current smoking) Exclusion criteria: Dipstick-positive proteinuria or established diabetic nephropathy; other severe renal disease; hyperkalemia; CHF; low ejection fraction; uncontrolled HTN; recent MI or stroke (<4weeks) and use of or hypersensitivity to vitamin E or ACE inhibitor Baseline data: 3577 patients with diabetes were included, mean age 65.4, 37% women, 63% men, 56% had history of hypertension	Groups: C: placebo Rx: ramipril 10 mg daily in the evening	Initial N: C: 1769 Rx: 1808 Final N: C: 184 (12%) Rx: 220 (15%) Compliance: 37% on ramipril and 37% on placebo stopped drug at any time; 33% on ramipril and 34% on placebo stopped drug by last visit	MI: C: 229 (12.9%) Rx: 185 (10.2%) RRR 22% (6,36); p=0.01 Stroke: C: 108 (6.1%) Rx: 76 (4.2%) RRR 33% (10,50); p=0.0074 CV death: C: 172 (9.7%) Rx: 112 (6.2%) RRR 37% (21,51); p=0.0001 Total Mortality: C: 248 (14%) Rx: 196 (10.8%) RRR 24% (8,37); p=0.004 RR 0.76 (0.67, 0.92) NNT 32 (19, 98) Overt Nephropathy (albumin/creatinine ratio ≥36 mg/mmol): C: 149 (8.4%) Rx: 117 (6.5%) RRR 24% (3,40); p=0.027 Side effect leading to discontinuation of therapy: Cough C: 37 pts Rx: 133 pts Hypotension/dizziness C: 24 Rx: 30 Angioedema C: 1 Rx: 5 Hypertension C: 100 Rx: 138	Low adherence rate (65%) may underestimate the benefit of ramipril

Table 10.18: Target Blood Pressure for Type 1 and 2 Diabetes *Summary of a Meta-Analysis from Clinical Evidence*

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96[33] **References of studies included in systematic review:** Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998; 317:713-720[39]; Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-713[41] Hansson L, 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. Lancet 1998;351:1755-1762[40]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 2 RCTs **Intervention:** UKPDS: ≤150/≤85 mmHg with atenolol or captopril vs. ≤180/≤105 mmHg HOT: diastolic bp ≤80 mmHg vs. bp ≤90 mmHg **Settings:** not stated Sample size range: UKPDS: 758 patients to tight control and 390 patients to less tight control 1503 patients with DM included **Duration of Trials:** 8.4 and 3.8 years	**Inclusion criteria:** UKPDS: blood pressure ≥160/90 if on no antihypertensive medications; ≥150/85 if uncontrolled on antihypertensive medications HOT: diastolic pressure between 110-115 mmHg **Age Range:** not stated	**Fatal or non-fatal MI:** ≤180/≤105 mmHg: 83/390 (21%) ≤150/≤85 mmHg: 107/758 (14%) NNT 14 (9,35) over 8.4 years **Fatal or non-fatal stroke:** ≤180/≤105 mmHg: 34/390 (8.7%) ≤150/≤85 mmHg: 38/758 (5%) NNT 27 (18,116) over 8.4 years **Fatal or non-fatal MI, stroke, or other CV death:** ≤90 mmHg: 45/501 (9%) ≤80 mmHg: 22/499 (4.4%) NNT 22 (16,57) over 3.8 years	No good evidence of a threshold below which it is harmful to lower blood pressure	Combination therapy is required to achieve target blood pressure Aggressive blood pressure lowering can reduce CV morbidity and mortality

Drug Therapy for Microalbuminuria in Normotensive Patients

Target Blood Pressure for People with Diabetes and Hypertension

Problem Formulation 11

Clinical Question:	Are ACEIs or ARBs recommended in normotensive patients with [diabetes and] microalbuminuria?"
Population:	Adults with type 1 and 2 diabetes, known microalbuminuria, and normal blood pressure
Health Intervention:	▪ ACE inhibitors ▪ Angiotensin receptor blockers
Most Important Health Outcomes:	▪ Progression to End State Renal Disease (ESRD) ▪ Dialysis
Side Effects of the Intervention:	▪ Persistent dry cough ▪ Rash ▪ Increased intermediate outcomes (e.g., azotemia, hyperkalemia, etc.)
Intermediate Outcomes	▪ Albumin excretion ▪ Progression and regression of microalbuminuria

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH] ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	07/2008 - 09/4/09	0/65
	("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND microalbuminuria[All Fields] AND normotensive[All Fields] AND (("2007/08/31"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	Randomized, controlled trial, All Adult: 19+ years, Human	08/31/07 - 09/4/09	2/5
PubMed	"Diabetic Nephropathies/drug therapy"[MeSH] OR "Albuminuria/drug therapy"[MeSH]	Randomized, controlled trial, All Adult: 19+ years, Human	08/31/07 -09/4/09	1/36
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05- 09/4/09	0/67

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
Clinical Evidence	No terms used - searched book section Endocrine and Metabolic Disorders, Conditions: Diabetes, Pregnancy and Childbirth	Systematic reviews and RCTs	7/15/05-09/4/09	0/0
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 07/2008	0/117
	"Diabetic Nephropathies/drug therapy"[MeSH] OR "Albuminuria /drug therapy"[MeSH]	Randomized, controlled trial, All Adult: 19+ years, Human	1965 – 08/31/07	1/133
	"Diabetic Nephropathies/drug therapy"[MeSH] AND "Albuminuria/drug therapy" [MeSH] AND "Angiotensin-Converting Enzyme Inhibitors"[MeSH] AND “hypertension”[MESH]	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 07/10/01	0/33
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Evidence Tables

ACE Inhibitor Effect on the Kidney in Normotensive Type 1 and 2 Diabetes

Table 11.1: Summary of Meta-Analysis from the Cochrane Database of Systematic Reviews

Author & Title	Last update & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)	Adverse Effects	Conclusions
Lovell HG. **Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria.** Cochrane Database Syst Revs. 2001 [60]	**Last update:** 11-29-2000 **Databases:** Medline **Search Terms:** Diabetes and ACE inhibitors; Diabetes and renal failure; Diabetes and microalbuminuria	**Number of studies included:** 12 RCTs, 1 meta-analysis **Intervention:** captopril 25-100 mg/day OR enalapril 5-20 mg/day lisinopril was used in one study **Settings:** not stated **Heterogeneity:** Mean arterial pressure of those on ACE inhibitor highly significantly heterogeneous Baseline albumin excretion rates (mg per day): not significantly heterogeneous at 134 vs. 129. Those measured in micrograms per minute were significantly heterogeneous at 96 vs. 115. End of study GHb showed significant heterogeneity ($p<0.025$) although values for ACE inhibitor and placebo were very close **Sample size range:** Often small (15-143) **Duration of Trials:** At least one year None of the studies lasted long enough to establish a relationship with end-stage renal failure	**Inclusion criteria:** Both insulin dependent and non-insulin dependent diabetics that were normotensive Most patients had microalbuminuria but some had overt albuminuria Onset of diabetes was always <41 years **Age Range:** 14-70	**GHb:** Pooled mean effect was just significant with an average fall from 8.89% to 8.85% for treated groups and rise from 8.71% to 8.74% in the control group **Albumin excretion:** The rate fell for patients on ACE inhibitors in 11 of 12 studies; estimated effect of ACE was highly significant ($p<0.001$) with fixed, random, weighted or standardized models used (effect seen in both type 1 and 2) All three types of ACE inhibitor significantly reduced albumin excretion rate vs. controls Captopril (in insulin dependent diabetes) increased the albumin rate in the placebo group 11.8% (-3.3, 29.1) and decreased the albumin rate in the treatment group 17.9% (-29.6, -4.3) p=0.004 **Nephropathy (persistent proteinuria, a decline in glomerular filtration rate and increased arterial blood pressure):** Enalapril ARR 42% during seven years (15%, 69%) (after an open follow-up extension of one study)	Persistent dry cough in 5% to 20% of patients and exacerbation of inflammations ACE inhibitor may affect potassium levels and should not be used in combination with potassium-sparing diuretics or potassium supplements	Inhibition of angiotensin converting enzyme can arrest and reduce albumin excretion rate in microalbuminuria normotensive diabetics. It is not possible to be certain that reduction of albumin excretion rate is due to a separate renal effect. A direct link with postponement of end-stage renal failure has not been demonstrated

Note: Comparisons that are not stated in the results column were not disclosed by the author.

References of Studies Included in the Cochrane Systematic Review of ACE Inhibitor in Normotensive People with Diabetes
Ahmand J, et al. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diabetes Care 1997; 20:1576-81. Bakris GL, et al. ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects. J Diab Comp 1994; 8:2-6. Bilo H, et al. Long-term use of captopril or nifedipine in normotensive microalbuminuria patients with insulin-dependent diabetes mellitus. Diabetes Research 1993; 23:115-122. Chase HP, et al. Angiotensin-converting enzyme inhibitor treatment for young normotensive diabetic subjects: a two-year trial. Ann Ophthamol 1993; 25:284-9. Hallab M, et al. Comparison of reduction in microalbuminuria by enalapril and hydrochlorothiazide in normotensive patients with insulin dependent diabetes. Br Med J 1993; 306: 175-82. Laffel L, et al. Captropril decreases the rate of progression of renal disease in normotensive insulin-dependent diabetes mellitus (IDDM) patients with microalbuminuria. J Am Soc Nephrol 1993; 3:304. Laffel L, et al. The beneficial effect of angiotensin-converting enzyme inhibition on diabetic nephropathy in normotensive, IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med 1995; 99(5):497-504. Marre M, et al. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. Br Med J 1988; 927:1092-5. Marre M, et al. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. Br Med J 1987; 294:1448-52. Mathiesen ER, et al. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. Br Med J 1991; 303:81-7. Parving HH, et al. Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. Br Med J 1989; 299:533-6 Ravid M, et al. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med. 1996 Feb 12; 156(3):286-9. Ravid M, et al. Plasma lipids and the progression of nephropathy in diabetes mellitus type II: effect of ACE inhibitors. Kidney Int. 1995 Mar; 47(3):907-10. Ravid M, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med. 1993 Apr 15; 118(8):577-81. Ravid M, et al. Long-term effect of ACE inhibition on development of nephropathy in diabetes mellitus type II. Kidney Int Suppl. 1994 Feb; 45:S161-4. Sano T, et al. Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: results of a 4-year, prospective, randomized study. Diabet Med. 1996 Feb; 13(2):120-4. Sano T, et al. Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. Diabetes Care. 1994 May; 17(5):420-4. Stornello M, et al. Angiotensin converting enzyme inhibition in normotensive type II diabetics with persistent mild proteinuria. J Hypertens Suppl. 1989 Dec; 7(6):S314-5. Hansen KW, et al. Effects of captopril on ambulatory blood pressure, renal and cardiac function in microalbuminuria type 1 diabetic patients. Diabete Metab. 1994 Sep-Oct; 20(5):485-93. Viberti G, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA. 1994 Jan 26; 271(4):275-9.

Table 11.2: Summary of a Meta-Analysis Published in Annals of Internal Medicine

Use of ACE Inhibitors in Non-Hypertensive Type 1 Diabetes with Microalbuminuria

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)	Adverse Effects	Conclusions
The ACE inhibitors in Diabetic Nephropathy Trialist Group. **Should All Patients with Type 1 Diabetes Mellitus and Microalbuminuria Receive Angiotensin-Converting Enzyme Inhibitors?** A Meta-Analysis of Individual Patient Data. Ann Intern Med. 2001;134:370-79 (61)	**Last update:** March 2001 **Databases:** Medline **Search Terms:** Diabetes and ACE inhibitors; Diabetes and renal failure; Diabetes and microalbuminuria	**Number of studies included:** 12 RCTs. The studies were placebo-controlled or included a non-interventional group. The studies consisted of at least 10 patients measuring albumin excretion at baseline and one or more follow-up visits. Follow-up had to be for at least 1 year. **Intervention:** captopril 12.5-50 mg BID OR lisinopril 10-20 mg/day OR enalapril 10-20 mg/day OR perindopril 2 mg/day OR ramipril 1.25-5 mg/day **Heterogeneity:** not stated **Total number of patients:** 698 **Sample size range:** 16-137 **Mean age range:** 32-48 years **Mean treatment duration:** 17-24 years **Duration of trials:** At least one year follow-up (range: 1-4 years) **Funding:** meeting support by Zeneca Pharmaceuticals	**Inclusion criteria:** Type 1 Diabetes Mellitus and non-hypertensive patients Patients had microalbuminuria or a baseline albumin excretion rate of 20-200 mcg/min **Primary outcome:** rate of change in log albumin excretion rate **Secondary outcomes:** absolute rates of progression to macroalbuminuria and regression to normoalbuminuria	**Albumin excretion:** Analysis of treatment effect at 2 years was restricted to trials with at least 2 years of follow-up data or 646 patients in 10 trials At 2 years, albumin excretion rate was 50.5% (29.2, 65.5; p<0.001) lower in the treatment group compared with the placebo group The estimated 2 year difference on baseline albumin excretion was 74.1% in patients with albumin excretion rates of 200 mcg/min and 17.8% in patients with albumin excretion rates of 20 mcg/min (p=0.04) There was no effect on the influence of other covariates (duration of DM, diastolic bp, HgA1c, age, sex) on the difference in albumin excretion rates at 2 years. **Progression to Macroalbuminuria:** Reduced in patients receiving ACE inhibitor OR 0.38 (0.25, 0.57) p<0.001 **Regression to Normoalbuminuria:** Increased in patients receiving ACE inhibitor OR 3.07 (2.15, 4.44) p<0.001	Not stated	Albumin excretion rates were reduced in normotensive, type 1 diabetic patients with microalbuminuria who received ACE inhibitor. There was a decrease in the progression of macroalbuminuria by approximately one third compared with placebo and an increase in regression to normoalbuminuria by approximately 3 times compared with placebo.

Note: Comparisons that are not stated in the results column were not disclosed by the author.

References of Studies Included in the Meta-Analysis of Individual Patient Data of ACE Inhibitors in Normotensive, Type 1 Diabetes:

Barnes LA, et al. The effect of three years of antihypertensive therapy on renal structure in type 1 diabetic patients with albuminuria. The European Study for the Prevention of Renal Disease in Type 1 Diabetes (ESPRIT). Diabetes [in press].
Bojestig M, et al. ACE-inhibition during two years did not improve U-albumin excretion rate in normotensive microalbuminuria IDDM patients [abstract]. The PRIMA Study Group. Diabetologia. 1997; 40(Suppl 1):A544.
Crepaldi G, et al. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. The Italian Microalbuminuria Study Group in IDDM. Diabetes Care. 1998; 21:104-10.
Ebbehoj E, et al. Early ACE-I intervention in microalbuminuria: 24h BP, renal function, and exercise changes [abstract]. Diabetologia. 1998; 41(Suppl1):A5.
Laffel LM, et al. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med. 1995; 99:497-504.
Marre M, et al. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. Br Med J 1988; 297:1092-5.
Mathiesen ER, et al. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. Br Med J 1991; 303:81-7.
O'Donnell MJ, et al. Placebo-controlled trial of lisinopril in normotensive diabetic patients with incipient nephropathy. J Hum Hypertens. 1993; 7:327-32.
Viberti G, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European microalbuminuria Captopril Study Group. JAMA. 1994; 271:275-9.
Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group. Lancet. 1997; 349:1787-92.
Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. Melbourne Diabetic Nephropathy Study Group. Br Med J. 1991; 302:210-6.
Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension. The ATLANTIS Study Group. Diabetes Care. 2000; 23:1823-9.

Table 11.3: Summary of 2009 Evidence

<table>
<tr><th>Name
Design</th><th>N</th><th>Baseline Characteristics</th><th>Duration of Intervention</th><th>Biases*</th><th>Results</th></tr>
<tr><td rowspan="20">Agha et al. 2009
Prospective RCT

Note that this is indirect evidence</td><td rowspan="20">N=383
Intervention: 193
Control: 190</td><td rowspan="20">Intervention (Losartan 50 mg/d)
Mean±SD
SBP (mmHg): 134.3±8.6
DBP (mmHg): 82.3±11.4
Serum creatinine (mg/dL): 1.2±0.3
Random blood sugar (mg/dL): 182.9±81.4
Fasting blood sugar (mg/dL): 122.5±41.7
Serum Potassium (mEq/L); 4.3±0.8
24 hour urinary microalbumin (md/dL): 101.9±21.7

Control (vitamin B12 mecobalamin 500 mcg/d)
SBP (mmHg): 136.2±7.9
DBP (mmHg): 82.6±10.1
Serum creatinine (mg/dL): 1.2±0.5
Random blood sugar (mg/dL): 192.9±67.4
Fasting blood sugar (mg/dL): 121.9±33.8
Serum Potassium (mEq/L): 4.9±0.9
24 hour urinary microalbumin (mg/dL): 104.7±26.3</td><td rowspan="20">6 months (2 month follow-up)</td><td rowspan="20">2,3</td><td colspan="3">Characteristics of Test Group at Baseline, After 6 Months of Losartan Use, and 2 months After End of Losartan Use</td></tr>
<tr><td>Lab / Physical Exam Characteristics</td><td>After 6 mos. of Losartan, Mean± SD (n = 171)</td><td>2 months after stopping losartan, Mean± SD (n = 142)</td></tr>
<tr><td>SBP (mmHg)</td><td>131.1±12.6</td><td>132.6±10.9</td></tr>
<tr><td>DBP (mmHg)</td><td>78.6±13.4</td><td>79.7±10.3</td></tr>
<tr><td>Serum creatinine (mg/dL)</td><td>1.3±0.4</td><td>1.3±0.3</td></tr>
<tr><td>Random blood sugar (mg/dL)</td><td>161.3±51.2</td><td>173.1±63.8</td></tr>
<tr><td>Fasting blood sugar (mg/dL)</td><td>112.5±26.5</td><td>115.8±31.1</td></tr>
<tr><td>Serum Potassium (mEq/L)</td><td>4.4±1.1</td><td>4.2±0.9</td></tr>
<tr><td>24 hour urinary microalbumin (md/dL)</td><td>47.5±12.9</td><td>91.8±17.3</td></tr>
<tr><td colspan="3">Characteristics of Control Group at Baseline, After 6 Months of Losartan Use</td></tr>
<tr><td colspan="2">Lab / Physical Exam Characteristics</td><td>After 6 mos. Mean± SD (n = 190)</td></tr>
<tr><td colspan="2">SBP (mmHg)</td><td>134.1±10.1</td></tr>
<tr><td colspan="2">DBP (mmHg)</td><td>81.3±9.4</td></tr>
<tr><td colspan="2">Serum creatinine (mg/dL)</td><td>1.3±0.3</td></tr>
<tr><td colspan="2">Random blood sugar (mg/dL)</td><td>178.7±58.2</td></tr>
<tr><td colspan="2">Fasting blood sugar (mg/dL)</td><td>119.7±24.8</td></tr>
<tr><td colspan="2">Serum Potassium (mEq/L)</td><td>4.6±1.1</td></tr>
<tr><td colspan="2">24 hour urinary microalbumin (mg/dL)</td><td>103.9±22.9</td></tr>
</table>

<table>
<tr><th>Name
Design</th><th>N</th><th colspan="4">Baseline Characteristics</th><th>Duration of Intervention</th><th>Biases*</th><th colspan="4">Results</th></tr>
<tr><td rowspan="20">Makino et al. 2007
Post-ad hoc analysis of RCT

Note that this is indirect evidence</td><td rowspan="20">N=163
Telmisartan 40 mg: 58
Telmisartan 80 mg: 51
Placebo: 54</td><td></td><td>Placebo</td><td>Rx 40 mg</td><td>Rx 80 mg</td><td rowspan="20">52 weeks (1.3 years mean follow-up)</td><td rowspan="20">2,3,4,5</td><td colspan="4">Effect of Telmisartan on Transition and Remission from Microalbuminuria at Last Observation</td></tr>
<tr><td>Age, years</td><td>59.5</td><td>61.5</td><td>61.3</td><td></td><td>Placebo</td><td>Telmisartan 40 mg</td><td>Telmisartan 80 mg</td></tr>
<tr><td>Male, %</td><td>81.5</td><td>79.3</td><td>72.5</td><td>N</td><td>54</td><td>58</td><td>51</td></tr>
<tr><td>BMI, kg/m^2</td><td>24.6 ±3.6</td><td>24.6 ±3.1</td><td>25.4 ±3.9</td><td>Transitions n, (%)</td><td>18 (33.3)</td><td>7 (12.1)**</td><td>5 (9.8)**</td></tr>
<tr><td>Weight, kg</td><td>65.8 ±11.5</td><td>64.6 ±10.1</td><td>65.6 ±11.9</td><td>Normalizations n, (%)</td><td>1 (1.9)</td><td>9 (15.5)**</td><td>10 (19.6)**</td></tr>
<tr><td>Duration of DM, years</td><td>9.6±7.3</td><td>9.1±8.4</td><td>7.7±7.3</td><td colspan="4">**Statistical difference from placebo group at p<0.01</td></tr>
<tr><td>SBP, mmHg</td><td>128±13.5</td><td>131±13.0</td><td>133±13.0</td><td colspan="4" rowspan="14"></td></tr>
<tr><td>DBP, mmHg</td><td>73±8.6</td><td>75±9.5</td><td>78±8.9</td></tr>
<tr><td>HbA1c, %</td><td>7.1±0.9</td><td>7.0±0.9</td><td>7.2±0.7</td></tr>
<tr><td>UACR, mg/g</td><td>164±40.3</td><td>173±50.6</td><td>168±48.6</td></tr>
<tr><td>Serum Cr, mg/dL</td><td>0.8±0.2</td><td>0.8±0.2</td><td>0.8±0.2</td></tr>
<tr><td>CCr, mL/min</td><td>93.1±22.7</td><td>94.7±22.5</td><td>100.9±37.0</td></tr>
<tr><td>Total cholesterol, mg/dL</td><td>196±30.7</td><td>192±28.5</td><td>196±37.5</td></tr>
<tr><td colspan="4">Pattern of drug usage, %</td></tr>
<tr><td>Insulin</td><td>40.7</td><td>31.0</td><td>43.1</td></tr>
<tr><td>Diet therapy</td><td>42.6</td><td>34.5</td><td>49.0</td></tr>
<tr><td>Hypoglycemic agents</td><td>72.2</td><td>84.5</td><td>74.5</td></tr>
<tr><td>Lipid lowering agents</td><td>31.5</td><td>34.5</td><td>41.2</td></tr>
<tr><td>Casas et al. 2005, Meta-Analysis 127 trials</td><td>N=73,514</td><td colspan="4">See body of rationale</td><td>Weighted mean follow-up 4.2 years</td><td>4</td><td colspan="4">See body of rationale</td></tr>
</table>

Lipid Management

Drug Therapy for Microalbuminuria in Normotensive Patients

Problem Formulation 12

Clinical Question:	Should all patients with diabetes be on a lipid lowering agent?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating adults with type 1 and 2 diabetes.
Population:	Adults with type 1 and 2 diabetes
Health Problem:	Diabetes (and risk of cardiovascular events associated with diabetes)
Health Intervention:	▪ Fibrates ▪ Statins ▪ Niacin (Nicotinic Acid) ▪ Bile Acid Sequestrants - Colestipol or Cholestyramine (Resins) ▪ No Drug Treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Angina ▪ Myocardial infarctions ▪ Stroke ▪ CHD mortality ▪ Total mortality ▪ CVD events

Side Effects of the Intervention:	▪ Exercise intolerance
	▪ Muscle pain
	▪ Weakness
	▪ Gastrointestinal effects
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Myositis
	  ▪ Rhabdomyolysis
	  ▪ Elevation in liver transaminases

Intermediate Outcome	▪ Myositis ▪ Elevation in liver transaminases ▪ Rhabdomyolysis

Lipid Management

Problem Formulation 13

Clinical Question:	What is the target low-density lipoprotein (LDL) cholesterol level for patients with diabetes without coronary heart disease (CHD)?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating adults with type 1 and 2 diabetes with established hyperlipidemia.
Population:	Adults with type 1 and 2 diabetes with known dyslipidemia
Health Problem:	Cardiovascular disease as a result of dyslipidemia
Health Intervention:	▪ Target LDL cholesterol goal of < 160 mg/dl ▪ Target LDL cholesterol goal of < 130 mg/dl ▪ Target LDL cholesterol goal of < 100 mg/dl ▪ No target All targets were compared with no target.
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit; inpatient hospital stay
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ CHD events ▪ First acute major coronary event

Side Effects of the Intervention:	▪ Exercise intolerance
	▪ Muscle pain
	▪ Weakness
	▪ Stomach pain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Myositis
	  ▪ Rhabdomyolysis
	  ▪ Elevation in liver transaminases

Intermediate Outcome	▪ Cholesterol levels

Lipid Management: LDL Goals

Problem Formulation 14

Clinical Question:	What is the target LDL cholesterol level for patients with diabetes with established CHD?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating adults with type 1 and 2 diabetes with established hyperlipidemia.
Population:	Adults with type 1 and 2 diabetes with known dyslipidemia
Health Problem:	Cardiovascular disease as a result of dyslipidemia
Health Intervention:	▪ Target LDL cholesterol goal of < 160 mg/dl ▪ Target LDL cholesterol goal of < 130 mg/dl ▪ Target LDL cholesterol goal of < 100 mg/dl ▪ No target All targets were compared with no target.
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit; inpatient hospital stay
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ CHD events ▪ First acute major coronary event

Side Effects of the Intervention:	▪ Exercise intolerance
	▪ Muscle pain
	▪ Weakness
	▪ Stomach pain
	▪ Headache
	▪ Increased intermediate outcomes:
	  ▪ Myositis
	  ▪ Rhabdomyolysis
	  ▪ Elevation in liver transaminases

Intermediate Outcome	▪ Cholesterol levels

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	((("hyperlipidemia"[Mesh terms] OR "dyslipidemia"[tw]) OR "hypercholesterolemia"[tw]) AND ((((((((((((((((((("drug therapy"[All Fields] OR "medicine"[Mesh terms]) OR "anticholesteremic agents"[Mesh terms]) OR "lovastatin"[Mesh terms]) OR "simvastatin"[Mesh terms]) OR "pravastatin"[mesh terms]) OR "atorvastatin"[text]) OR "fluvastatin"[text]) OR "gemfibrozil"[mesh terms]) OR "Fibric Acid Derivatives"[text]) OR "Fibrates"[text]) OR "cholestyramine"[mesh terms]) OR "Colestipol"[mesh terms]) OR "Bile Acid Sequestrants"[text]) OR "Resins"[text]) OR "niacin"[mesh terms]) OR "Nicotinic Acid"[text]) AND "meta-analysis"[pt]) AND "human"[mesh terms]) AND "adult"[mesh terms]) AND "Diabetes Mellitus"[mesh]))	Meta-analysis, All Adult: 19+ years, English, Human	1/1/66 – 6/4/02	1/25
			6/4/02 – 5/1/06	0/0
		Randomized Controlled Trial, All Adult: 19+ years English, Human	1/1/66 – 7/16/02	0/163
			7/16/02 – 5/1/06	0/89
PubMed	((("hyperlipidemia"[Mesh terms] OR "dyslipidemia"[tw]) OR "hypercholesterolemia"[tw]) AND ((((((((((((((((((("drug therapy"[All Fields] OR "medicine"[Mesh terms]) OR "anticholesteremic agents"[Mesh terms]) OR "lovastatin"[Mesh terms]) OR "simvastatin"[Mesh terms]) OR "pravastatin"[mesh terms]) OR "atorvastatin"[text]) OR "fluvastatin"[text]) OR "gemfibrozil"[mesh terms]) OR "Fibric Acid Derivatives"[text])OR "Fibrates"[text]) OR "cholestyramine"[mesh terms]) OR "Colestipol"[mesh terms]) OR "Bile Acid Sequestrants"[text]) OR "Resins"[mesh terms]) OR "niacin"[mesh terms]) OR "Nicotinic Acid"[text]) AND "meta-analysis"[pt]) AND "human"[mesh terms]) AND "adult"[mesh terms]))	Meta-analysis, All Adult: 19+ years, English, Human	7/20/00 – 2/20/04	0/8
			2/20/04 – 5/1/06	0/3
		Randomized Controlled Trial, All Adult: 19+ years English, Human	7/20/00 – 2/20/04	1/201
			2/20/04 – 5/1/06	1/267

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
Cochrane	"(Drug OR statin OR fibrate OR niacin OR colestipol OR cholestyramine) AND (hyperlipidemia OR dyslipidemia OR hypercholesterolemia) AND diabetes"	Systematic reviews	None applied	0/10
			Searched 5/1/06	0/42
	drug AND (primary prevention OR secondary prevention) AND (hyperlipidemia OR dyslipidemia OR hypercholesterolemia)"	Systematic reviews	None applied	0/4
			Searched 5/1/06	0/12
Clinical Evidence	"diabetes AND (statin OR fibrate OR niacin OR colestipol OR cholestyramine)" via on-line search field	Systematic reviews and RCTs	Searched 5/30/02; 4/6/04; 5/1/06	3/7

Note:

- Initial studies reviewed included only systematic reviews and meta-analyses from Clinical Evidence, Cochrane, and PubMed. The PubMed searches for RCTs were conducted to update the systematic reviews found in Clinical Evidence and Cochrane Database of Systematic Reviews (3rd quarter, 2002).
- Intermediate health outcome trials such as REVERSAL and trials involving rosuvastatin, which have demonstrated reductions in LDL-C, have been excluded because they did not measure direct health outcomes. Only studies where direct health outcomes were evaluated have been included.
- One study, CARDS (Colhoun et al., 2004),[70] was published after the search and was included in the review of evidence.

Evidence Tables

Table 14.1: Lipid-Lowering Drugs for Primary Prevention of Cardiovascular Events

Meta-Analysis from Clinical Evidence Author &Title	Last Update & Search Database	Study Characteristics	Results (95% Confidence Interval)	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence Volume 9, May 2003 **References of studies included in the systematic review:** Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. American J Med 2001; 111:633–642. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care 1998; 21:641–648. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.	Last update: April 2002 Databases: Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE Search Terms: Not stated	**Inclusion criteria:** Huang Meta-Analysis**:** ≥18 years; more than 10 patients in each trial arm; comparison of intensive risk factor reduction using drug therapy vs. placebo, or routine risk factor reduction; at least 1 year of follow-up; presentation of treatment effect on risk factor levels; and report of at least one prespecified outcome SENDCAP: type 2 diabetes, aged 35–65 years, any of the following in at least one screening sample: serum cholesterol ≥5.2 mmol/l, serum triglyceride≥1.8 mmol/l, HDL cholesterol ≤1.1 mmol/l, and total-to-HDL cholesterol ratio≥4.7 HPS: age 40–80 years, total cholesterol concentrations ≥3·5 mmol/L, 5-year risk of death from coronary heart disease because:(i) coronary disease or (ii) occlusive disease of non-coronary arteries or (iii) diabetes mellitus (type 1 or type 2); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories). **Number of studies included:** 1 systematic review and 2 RCTs with at least 10 confirmed clinical cardiovascular events among people with diabetes. Studies reporting only intermediate end points (e.g., regression of plaque on angiography, lipid changes) were not included. **Intervention:** lovastatin or gemfibrozil vs. placebo bezafibrate vs. placebo simvastatin vs. placebo **Sample size range:** 135-5963 **Duration of Trials:** 3-5.0 years	**Huang Meta-Analysis** Pooled 2 RCTs (AFCAPS/TexCAPS, Helsinki; 290 people with diabetes, mean age 49 and 58 years) comparing lovastatin vs. gemfibrozil vs. placebo for 5 years Lovastatin or gemfibrozil vs. placebo decreased (not statistically significant) non-fatal MI and CAD mortality [8 vs. 19 events/1000 years; RR 0.44 (0.17-1.20)] **SENDCAP** 164 men and women with type 2 diabetes, age 35-65 years, 3 year follow-up bezafibrate vs. placebo significantly reduced MI or new ischemic changes on EKG [5/64 (7.8%) vs. 16/64 (25%); RR 0.31; NNT 6, 95% CI 5 to 20)] **HPS** 5963 men and women with diabetes, aged 40-80 years, 3982 with no previous CHD Significant decrease in outcomes (all-cause mortality, non-fatal MI, coronary heart disease death, total stroke, or any revascularization) with simvastatin vs. placebo Results similar for people with diabetes and previous CHD and for people with diabetes and NO previous CHD Diabetes and previous CHD: [325/972(33.4%) with simvastatin vs. 381/1009 (37.8%) with placebo; RR 0.89, ARR 4.3%, NNT 23, 95%CI 12 to 897] Diabetes and no prior CHD: [276/2006 (13.8%) with simvastatin vs. 367/1976 (18.6%) with placebo; RR 0.74, ARR 4.8%, NNT 21, 95% CI 14 to 40]	HPS provides the first clear evidence that statin treatment is effective for primary prevention of cardiovascular disease in patients with diabetes

Table 14.2: Lipid-Lowering Drugs for Secondary Prevention of Cardiovascular Events Meta-Analysis from Clinical Evidence

Author &Title	Last update Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 (33) **References of studies included in the systematic review:** Pyorala K, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) Diabetes Care. 1997;20(4):614-20 (71) Sacks FM, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001-9 (141) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339(19):1349-57 (72) Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410-18 (142)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** 4 RCTs that included at least 10 confirmed clinical cardiovascular events among people with diabetes (studies reporting only intermediate end points were not considered) **Intervention:** simvastatin (20 mg QD then 40 mg QD depending on initial response) vs. placebo pravastatin (40 mg QD) vs. placebo (2 studies) gemfibrozil (1200 mg) **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 2531-9014 patients (202-782 diabetics in subpopulations) **Duration of Trials:** 5-6.1 years	**Inclusion criteria:** One study only included men 3-20 months after MI and total cholesterol <6.2 mmol/l (238.4 mg/l), triglycerides <3.92 mmol/l (343.8 mg/l), and LDL 3.0-4.5 mmol/l (115.3-173.0 mg/l) AMI unstable angina, or total cholesterol 4-7 mmol/l (153.8-269.2 mg/l) AND triglycerides <5 mmol/l (438.5 mg/l) Previous MI or angina AND total cholesterol 5.5-8 mmol/l (211.5-307.6 mg/l) and triglycerides≤2.5 mmol/l (219.2 mg/l) CVD, MI, angina, revascularization, OR angiographical documented coronary stenosis AND HDL ≤1 mmol/l (38.46 mg/l), LDL ≤3.6 mmol/l (138.4 mg/l) OR triglycerides ≤3.4 mmol/l (298.2 mg/l) **Age Range:** 21-75	**CHD death or non fatal AMI:** pravastatin RR 0.84 (0.59, 1.0) NNT 28 gemfibrozil RR 0.76 (0.57, 1.0) NNT 13 (7, 144) **Major CV event:** pravastatin RR 0.75 (0.57, 1.0) NNT 12 (7, 194) simvastatin RR 0.45 (0.27, 0.74) NNT 5 (3, 5) **RR total mortality:** simvastatin 0.63 (0.43, 0.92)	None noted	Most studies with significant power to detect cardiovascular events have enrolled low numbers of diabetics and therefore were not included in this systematic review Statins and fibrates are effective in secondary prevention of cardiovascular disease in people with diabetes and dyslipidemia

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 14.3: Lipid-Lowering Drugs for Prevention of Cardiovascular Events *RCT*

Study, Total n	Treatment Groups Size & Drug	Study Population	Results	Comments
Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003 Jun 14; 361(9374):2005-16. (RCT) Follow-up: Mean duration- 4.8	Treatment Group (Diabetes subgroup, n= 2,978) Simvastatin 40 mg daily Control Group: (Diabetes subgroup, n=2,985) Placebo daily	Patient eligibility criteria: Men and women 40-80 years Non fasting blood chol >3.5 mmol/L (135mg/dL) History of diabetes; coronary disease; occlusive disease of non-coronary arteries; treated HTN Baseline characteristics: Diabetes and no prior CHD (n= 1981) Diabetes and other CVD (n= 1110) Diabetes and no CVD (n= 2912)	Major Vascular Events — Simvastatin / Placebo / RRR Diabetes: 601(20.2%) / 748 (25.1%) / 22% (13-30, p<0.0001) Total: 2033 (19.8%) / 2585 (25.2%) / 24% (19-28, p<0.0001) Diabetes: No CVD: 135 (9.3%) / 196 (13.5%) / 33% (17-46, p<.0003) Diabetes: LDL<3.0: 191(15.7%) / 252 (20.9%) / 27% (1340, p = 0.0007) The proportional risk reduction was about a quarter among various other studies ofsubcategories of diabetic patients, including: those with different duration, type or control of diabetes; those aged over 65 years at entry or with hypertension; and those with total cholesterol below 5.0 mmol/L. Among participants who had a first major vascular event following randomization, allocation to simvastatin reduced the rate of subsequent events during the scheduled treatment period.	40 mg of simvastatin daily reduces risk of heart attack and stroke among patients with diabetes

Table 14.4: Summary of Randomized, Controlled Trials of Lipid-Lowering Pharmacotherapy in Subjects with Diabetes Mellitus

Study, Total n (n DM subgroup*)	Treatment Groups Size & Drug (mg/dl – dose per day)	Baseline LDL, mg/dl	% Change in LDL (from baseline)	On-Trial LDL, mg/dl†	Coronary Events Absolute (ARR) & Relative (RR) Reduction, 95% CI	NNT	Follow-up
Primary Prevention							
Helsinki Heart, 4081 (135) (subgroup analysis)	Rx: 59, gemfibrozil 1200 C: 76, placebo	200 ± 35 202 ± 32	-10% -6%	180 190	Rx: 3.4% C: 10.5% ARR: 7.1% P=0.19 (nonfatal MI/CHD death)	N/A	5 yrs
SENDCAP, 164 (164)	Rx: 81, bezafibrate 400 C: 83, placebo	142 (126, 174) 154 (128, 173)	-9.6% (-17.6, 4.2) +0.6 (-12.9, 10.8)	128 (112, 149) 152 (115, 173)	Rx: 7.4% C: 21.0% ARR: 13.6% P=0.01 (MI or probable ischemia)	8	5 yrs
Secondary Prevention							
4S, 4444 (Haffner, 483)‡ (subgroup analysis)	Rx-DM: 251, simvastatin 20-40, C-DM: 232, placebo	190 ± 26 189 ± 26	-36% +4%	122 197	Rx: 23.5% C: 37.5% ARR: 14% RR: 0.58 (0.41, 0.80) P=0.001 (major coronary events)	7	5 yrs
Abbreviations: DM: diabetes dx by hx and FBS IFG: impaired fasting glucose NFG: normal fasting glucose	Rx-IFG: 343 C-IFG: 335	189 ± 26 188 ± 25	-36% +5%	121 197	Rx: 19.5% C: 30.4% ARR: 11% RR: 0.62 (0.46-0.85) P=0.003	8	
	Rx-NFG: 1606 C-NFG: 1631	188 ± 26 189 ± 26	-38% +3%	117 195	Rx: 18.6% C: 26.2% ARR: 7.6% RR: 0.68 (0.59-0.79) P=0.003	12	
4S (Pyorala, 202)§	Rx: 105	186 ± 25	-36%	119	Rx: 22.9% C: 45.4% ARR: 22.5% RR: 0.45 (0.27-0.74) P=0.002 (major CHD event)	4	5 yrs
(subgroup analysis)	C: 97	186 ± 27	n/r				
CARE, 4159 (586) (subgroup analysis)	Rx: 282, pravastatin 40 C: 304, Placebo	136 ± 14 (same as Rx)	-27% n/r	99 ± 21	Rx: 17.7% C: 20.4% ARR: 2.7% RR: 0.85 (0.58, 1.2) (MI or CHD death)	N/A	5 yrs
					Rx: 28.7% C: 36.8% ARR: 8.1% RR: 0.75 (0.58,1.0) P=0.05 (expanded endpoints)**	12	

* Table includes only studies in which data was reported separately for subjects with diabetes.

† On-trial LDL calculated from published data.

‡ Haffner included expanded definition of diabetes (by fasting blood glucose levels).

§ Pyorala included diabetes by history only.

** Expanded endpoints: CHD death, nonfatal MI, CABG, PTCA

Table 14.5: Treatment Strategy for Lipid Lowering in People with Diabetes Mellitus (Primary Prevention) (adapted from CMI Diabetes Guideline 2002)

Author & Title	Last Updated Search Database	Study Characteristics	Results	Conclusions	Comments/ Biases
Sigal R, Meggison H, and Malcolm J. What are the effects of treating hyperlipidaemias in people with diabetes? Clinical Evidence, Issue 7, October 2002 (on-line version) References of studies included in the systematic review: Downs JR, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/ Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279(20):1615-22. Koskinen P, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. Diabetes Care. 1992 Jul;15(7):820-5 (66) Elkeles RS, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care. 1998 Apr;21(4):641-8 (67)	LAST UPDATED: August 2001 SEARCH DATABASES AND SEARCH STRATEGY: Systematic Reviews - Cochrane Library CD, Medline and Embase RCTs - Cochrane Controlled Clinical Trials Register, Best Evidence CD, Medline and Embase looking back at least 3 years, or to their origin if there are no systematic reviews SEARCH TERMS: Not stated.	STUDY DESIGN Qualitative systematic review Inclusion criteria: AFCAPS/TexCAPS included men aged 45–73 years and women aged 55–73 years, with TC 178.8-262.3 mg/L, LDL-C 129.2-188.8 mg/L, HDL-C ≤42.3 mg/L (men) or ≤46.92 mg/L (women), and TGs ≤369.5 mg/L. HELSINKI included 4081 Finnish men aged 40–55 years with a lipid concentration (minus HDL-C) ≥201 mg/dL. SENDCAPS included 164 men and women with type 2 Diabetes, aged 35–65 years. Participants had TC to HDL ratio greater than 4.7 mmol/L (180.7 mg/L), TC ranged from 201 mg/L, HDL-C less than 1.1 mmol/L (42.3 mg/L). Number of studies included: 3 RCTs that included at least 10 confirmed clinical cardiovascular events among people with diabetes (studies reporting only intermediate end points were not considered) Intervention: lovastatin vs. placebo plus diet bezafibrate vs. placebo gemfibrozil (600 mg BID) vs. placebo Sample size range: 135-164 Duration of Trials: 3-5.2 years	Primary Prevention In the first RCT (AFCAPS/TexCAPS), men aged 45–73 years and women aged 55–73 years were randomized to diet plus lovastatin 20–40 mg daily or diet plus placebo, and followed for a mean of 5.2 years. (cardiovascular events rate: 4.8% vs. 8.5%; RR 0.56) The second RCT (Helsinki) that included 4081 Finnish men aged 40–55 years compared gemfibrozil 600 mg twice daily vs. placebo over 5 years. (cardiovascular events rate: 3.4% vs. 10.5%; RR 0.33) The third RCT (SENDCAP) that included 164 men and women with type 2 diabetes, aged 35–65 years, compared bezafibrate vs. placebo for 3 years. (cardiovascular events rate: 7.8% vs. 25%; RR 0.31) (95% CI and P values were not reported. It is uncertain whether the reported results reached statistical significance.) Mixed Primary and Secondary Prevention: There is one RCT (the Diabetes Atherosclerosis Interventions Study) that included 305 men and 113 women, with mean age 57 years and type 2 diabetes. The trial compared the effect of fenofibrate 200 mg daily vs. placebo in type 2 diabetes for a minimum of 3 years. After 39 months on treatment and 6 additional months of follow-up, fenofibrate vs. placebo did not significantly reduce the number of patients who either had myocardial infarction or died. [15/207 (7.2%) with fenofibrate v 21/211 (9.9%) with placebo; ARR 2.7%, 95% CI –2.8% to +8.3%; RR 0.73, 95% CI 0.39 to 1.37].	From the available subgroup data for primary prevention, fibrates appeared to be more effective than statins in lowering cardiovascular event rate. However, 95% CI and P values were not reported. It is uncertain whether the reported results reached statistical significance. Results for "mixed primary and secondary prevention" did not reach statistical significance.	SENDCAP only included type 2 diabetics and Helsinki only included men. Most studies with significant power to detect cardiovascular events have enrolled low numbers of diabetics and therefore were not included in this systematic review.

Table 14.6: Treatment Strategy for Lipid Lowering in People with Diabetes Mellitus (Secondary Prevention) (adapted from CMI Diabetes Guideline 2002)

Author & Title	Last Updated Search Database	Study Characteristics	Results	Conclusions	Comments/ Biases
Sigal R, Meggison H, and Malcolm J. What are the effects of treating hyperlipidaemias in people with diabetes? Clinical Evidence, Issue 7, October 2002 (on-line version) References of studies included in the systematic review: Pyorala K, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) Diabetes Care. 1997;20(4):614-20 (71) Sacks FM, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001-9 (141) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339(19):1349-57 (72) Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410-18 (142)	LAST UPDATED: August 2001 SEARCH DATABASES AND SEARCH STRATEGY: Systematic Reviews - Cochrane Library CD, Medline and Embase RCTs - Cochrane Controlled Clinical Trials Register, Best Evidence CD, Medline and Embase looking back at least 3 years, or to their origin if there are no systematic reviews SEARCH TERMS: Not stated.	STUDY DESIGN Qualitative systematic review Number of studies included: 4 RCTs that included at least 10 confirmed clinical cardiovascular events among people with diabetes (studies reporting only intermediate end points were not considered) Inclusion criteria: 4S - 4444 men and women aged 35–70 years with previous acute MI or angina pectoris, TC concentrations of 5.5–8.0 mmol/L, and TGs < 2.5 mmol/L. CARE - 4159 men and women aged 21–75 years, 3–20 months after acute MI and with TC < 6.2 mmol/L, TGs < 3.92 mmol/L, and LDL-C 3.0–4.5 mmol/L. LIPID - 9014 men and women aged 31–75 years with acute MI or unstable angina, plasma TC 4.0–7.0 mmol/L, and plasma TGs < 5.0 mmol/L. VA-HIT - 2531 men aged < 74 years with previous coronary vascular disease, acute MI, angina, revascularisation, or angiographically documented coronary stenosis; HDL-C < 1.0 mmol/L, LDL-C < 3.6 mmol/L, and TGs < 3.4 mmol/L. Intervention: simvastatin (20 mg QD then 40 mg QD depending on initial response) vs. placebo pravastatin (40 mg QD) vs. placebo pravastatin (40 mg QD) vs. placebo gemfibrozil (1200 mg) Sample size range: 2531-9014 patients (202-782 diabetics in subpopulations) Duration of Trials: 5-6.1 years	4S compared simvastatin vs. placebo over a median of 5.4 years. The relative risk of main end points in people with diabetes treated with simvastatin were as follows: Total mortality 0.57 (95% CI 0.30 to 1.08); Major cardiovascular events 0.45 (95% CI 0.27 to 0.74); Any atherosclerotic event 0.63 (95% CI 0.43 to 0.92). CARE compared pravastatin 40 mg daily vs. placebo over a median of 5 years. Among the people with diabetes, the relative risk of major coronary events (death from coronary disease, nonfatal acute MI, coronary artery bypass graft, or PTCA) = 0.75 (95% CI 0.57 to 1.0). LIPID compared pravastatin 40 mg daily vs. placebo for a mean of 6.1 years. Among the 782 participants with diabetes, the relative risk of CHD death or nonfatal acute MI = 0.84 (95% CI 0.59 to 1.10). VA-HIT compared gemfibrozil 1200 mg daily with placebo for a median of 5.1 years (treatment was intended to raise HDL-C levels rather than reduce LDL-C). Among the 627 participants with diabetes, the relative risk of CHD death or nonfatal acute MI =0.76 (95% CI 0.57 to 1.0).	From the available data for secondary prevention, statins and fibrates were shown to be essentially the same in their effectiveness in significantly reducing the rate of CAD events in the diabetes mellitus population.	Most studies with significant power to detect cardiovascular events have enrolled low numbers of diabetics and therefore were not included in this systematic review.

Drug Therapy for Primary and Secondary Prevention of Cardiovascular Events in the General Diabetes Population

ACE Inhibitor Therapy for Prevention of Cardiovascular Disease (CVD)

Problem Formulation 15

Clinical Question:	Should all patients with diabetes be on ACE inhibitors?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in the use of ACE inhibitors in primary prevention of cardiovascular disease in people with diabetes.
Population:	All adults with type 1 and 2 diabetes with and without a documented cardiovascular event
Health Problem:	Diabetes and the risk of cardiovascular events
Health Intervention:	▪ ACE inhibitor ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ Fatal or non-fatal MI ▪ Fatal or non-fatal stroke
Side Effects of the Intervention:	▪ Cough ▪ Dizziness ▪ Angioedema
Intermediate outcomes:	▪ Hypotension ▪ Hypertension

Aspirin Therapy in Diabetes for Prevention of CVD

Problem Formulation 16

Clinical Question:	Should all patients with diabetes be on aspirin?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in the use aspirin in primary and secondary prevention of cardiovascular disease in people with diabetes.
Population:	All adults with type 1 and 2 diabetes with and without a documented CV event
Health Problem:	Diabetes and the risk of cardiovascular events
Health Intervention:	▪ Aspirin ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ Fatal or non-fatal MI
Side Effects of the Intervention:	▪ Fatal bleeds ▪ Stroke ▪ Minor bleeds ▪ GI symptoms

Beta-Blocker Therapy for Secondary Prevention of CVD

Problem Formulation 17

Clinical Question:	Should all patients with prior cardiovascular events be on beta-blockers?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in the use beta-blockers for secondary prevention of cardiovascular events in people with diabetes.
Population:	All adults with type 1 and 2 diabetes with and without a documented CV event
Health Problem:	Diabetes and the risk of cardiovascular events
Health Intervention:	▪ Beta-blockers ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ Fatal or non-fatal MI
Side Effects of the Intervention:	▪ Weight gain

Glucose Control

Problem Formulation 18

Clinical Question:	Should a multifactorial approach to decreasing cardiovascular disease with simultaneous treatment of risk factors be used in patients with diabetes?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating patients with type 1 and 2 diabetes
Population:	Adults with type 1 and type 2 diabetes
Health Problem:	Diabetes and the risk of cardiovascular events
Health Intervention:	▪ Intensive therapy aimed at multiple risk factors ▪ Conventional therapy
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, and pharmacists
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Cardiovascular events ▪ Mortality ▪ Nephropathy ▪ Retinopathy ▪ Autonomic Neuropathy

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Cardiovascular Diseases /prevention and control" [MeSH] AND "Diabetes Mellitus"[MeSH])	Meta-analysis, All Adult: 19+ years, English, Human	1/2001 – 08/2008	0/13
	"Cardiovascular Diseases /prevention and control" [MeSH] AND "Diabetes Mellitus"[MeSH])	Randomized, controlled trial, All Adult: 19+ years English, Human	1/2001 – 08/2008	2/260
	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/15/05	0/50
	(((((("Diabetes Mellitus /drug therapy"[MESH] AND "Heart Diseases/prevention and control"[MESH])	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 8/9/2001	1/11
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	1/1

Evidence Tables

Table 18.1: Summary of New Evidence- 2005 Search

Study	Inclusion & Exclusion Criteria	Age	Limitations / Biases	Intervention & dose – N and Final N	Duration	Outcome	Relative Risk (RR) or Hazard Ratio (HR) 95% CI	NNT	p value
ASA- Primary Prevention									
Sacco (2003) RCT	Diabetes patients without history of major cardiovascular events	≥50	Low statistical power due to premature stop. Open label study	I. aspirin (100 mg/d) - II no aspirin (10 mg/d) – N=1031 (DM subgroup) At end of study, 11.9% of DM patients in control group were taking aspirin, while 28.2% of aspirin patients had discontinued treatment	3.7 yrs median	Main endpoint [CV and cerebrovascular events (CV death, nonfatal MI, and nonfatal stroke) aspirin vs. no aspirin Total Cardiovascular Events aspirin vs. no aspirin Cardiovascular Death aspirin vs. no aspirin	 0.90(0.50-1.62) 0.89 (0.62-1.26) 1.23(0.69-2.19)	 - - -	 NS NS NS
ASA- Secondary Prevention									
Antithrombotic Trialists Collaboration (2002) Meta Analysis	All trials by 1996 that compared antiplatelet regimen with a control or another antiplatelet regimen among high-risk patients for vascular events.	N/A		Antiplatelet therapy vs. no antiplatelet therapy N=4961 (DM plus CVD subgroup) 9 trials with data		combined risk of non-fatal myocardial infarction, non-fatal stroke, death from a vascular cause, or death from an unknown cause antiplatelet vs. control	0.94 (0.83-1.07)	-	NS

Table 18.2: Effect of ACE Inhibitors on Mixed Primary and Secondary Prevention of CV Outcomes in People with Diabetes (HOPE study) *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Safety	Bias
Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE and MICR-HOPE substudy. Lancet 355(9200);2000:253-259 (32) Location: 19 countries in N & S America and Europe (Argentina, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, Netherlands, Norway, Spain, Switzerland, U.K., and U.S.A.) Sponsor: Funding from Medical Research Council of Canada; Hoecst-Marion Roussel; AstraZeneca; King Pharmaceuticals; Natural Source Vitamin E Association; NEGMA and the heart and Stroke Foundation of Ontario	Type of study: RCT Blinding: Originally blinded, then changed to open label at 4 years Follow-up: 4.5 years (stopped 6 months early due to efficacy)	Inclusion criteria: With or without diabetes; age 55 years or older; history of cardiovascular disease (CAD, stroke, or PVD) or diabetes plus at least one other CV risk factor (Tchol >5.2 mmol/L, HDL <=0.9 mmol/L, hypertension, known microalbuminuria, or current smoking) Exclusion criteria: Dipstick-positive proteinuria or established diabetic nephropathy; other severe renal disease; hyperkalemia; CHF; low ejection fraction; uncontrolled HTN; recent MI or stroke (<4weeks) and use of or hypersensitivity to vitamin E or ACE inhibitor Baseline data: 3577 patients with diabetes were included, mean age 65.4, 37% women, 63% men, 56% had history of hypertension	Groups: C: placebo Rx: Ramipril 10 mg daily in the evening	Initial N: C: 1769 Rx: 1808 Final N: C: 184 (12%) Rx: 220 (15%) Compliance: 37% on ramipril and 37% on placebo stopped drug at any time; 33% on ramipril and 34% on placebo stopped drug by last visit	MI: C: 229 (12.9%) Rx: 185 (10.2%) RRR 22% (6,36); p=0.01 Stroke: C: 108 (6.1%) Rx: 76 (4.2%) RRR 33% (10,50); p=0.0074 CV death: C: 172 (9.7%) Rx: 112 (6.2%) RRR 37% (21,51); p=0.0001 Total Mortality: C: 248 (14%) Rx: 196 (10.8%) RRR 24% (8,37); p=0.004 RR 0.76 (0.67, 0.92) NNT 32 (19, 98)	Side effect leading to discontinuation of therapy: Cough C: 37 pts Rx: 133 pts Hypotension/dizziness C: 24 Rx: 30 Angioedema C: 1 Rx: 5 Hypertension C: 100 Rx: 138	Low adherence rate (65%) may underestimate the benefit of ramipril

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 18.3: Effect of Aspirin on Cardiovascular Disease in Type 1 & 2 Diabetes (Primary & Secondary Prevention)

Author & Title	Last updated & Search Database	Study Characteristics	Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 [33] **References of studies included in systematic review:** Final Report on the aspirin component of the ongoing physicians' health study. Steering committee of the physicians' Health Study Research Group. N Engl J Med 1989;321(3):129-35 [76] Hansson L, 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. Lancet 1998;351:1755-1762 [40] ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. JAMA 1992;268:1292-1300 [77] Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81-106 [78]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included:** Primary prevention: 2 RCTs Mixed primary and secondary prevention: 1 RCT Secondary prevention: 1 systematic review **Intervention:** Aspirin vs. placebo Study #1: aspirin 325 mg QOD Study #2: aspirin 75 mg/day Study #3: 650 mg/day Review: 75-1500 mg/day **Settings:** Study #1- US; #2 International (26 countries) #3 US, multicenter **Sample size range:** 533 US male physicians with DM; unspecified number of pts with DM; 3711 men and women with DM (30% type1 and 48% prior CVD) **Duration of Trials:** After 5 years (studies #1 and 3); others unspecified	**Inclusion criteria:** Study #1 – US male physicians aged 40-85 years – subgroup analysis for DM pts ; #2 – Unspecified; #3 – DM diagnosis **Age Range:** 40-85 years (#1); unspecified	**Primary prevention of fatal or non-fatal MI among DM subset (325 mg QOD):** Placebo: 26/258 (10.1%) Aspirin: 11/275 (4%) RR 0.39 (0.20, 0.79) NNT 16 (12,47) over 5 years **Primary prevention of fatal or non-fatal MI (75 mg/day):** Aspirin reduced AMI to a similar degree in the subgroup of people with DM and in the overall total population (RR 0.85) **Primary and Secondary Prevention of fatal or non-fatal MI (650 mg/day):** Placebo: 336/1855 (18.1%) Aspirin: 289/1856 (15.6%) ARR 2% (0.1, 4.9%) NNT 50 **Overall Mortality (650 mg/day)** RR 0.91 (0.75, 1.11) p=ns	**Fatal or non-fatal stroke (650 mg/day):** Placebo: 4.2% Aspirin: 5% p=ns **All GI symptoms except ulcer (325 mg QOD):** Placebo: 34.2% Aspirin: 34.8% p=ns **Ulcer (325 mg QOD):** Placebo: 138 pts Aspirin: 169 pts (RR 1.22; 95%CI 0.98, 1.53;p=0.08) **Ulcer (hemorrhage) (325 mg QOD):** Placebo: 22 pts Aspirin: 38 pts (RR 1.78;95%CI 1.07, 2.94;p=0.04) **Bleeding (e.g., easy bruising, hematemesis, melena, non-specific GI, etc) (325 mg QOD):** Placebo: 2248 pts Aspirin: 2979 pts (RR 1.32; 95% CI 1.25, 1.40;p<0.00001) Doses higher than 325mg/day increased risk without improving efficacy Only 2% in both groups comparing 650mg/day **Fatal Bleeds (75 mg/day – DM not separated out):** Placebo: 8 pts Aspirin: 7 pts **Non-fatal major bleeds (75 mg/day– DM not separated out):** Placebo: 70 pts Aspirin: 129 pts **Minor bleeds (75 mg/day– DM not separated out):** Placebo: 87 pts Aspirin: 156 pts	Very large RCTs of primary and mixed secondary prevention, and a systematic review of secondary prevention, support a cardioprotective role for aspirin There is insufficient evidence to define precisely which people with diabetes should be treated with aspirin Risk of CVD is very low before age 30 Most white diabetic adults over 30 are at increased risk of CVD Aspirin doses ranged considerably per study Higher doses of aspirin did not necessarily correlate with increased reports of bleeding events

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 18.4: Effects of Beta-Blockers on Secondary Prevention of CV Outcomes in People with Non-Insulin-Dependent Diabetes *Summary of a RCT*

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Jonas M, et al. **Usefulness of beta-blocker therapy inpatients with non-insulin-dependent diabetes mellitus and coronary artery disease.** Am J Cardiol. 1996;77:1273-77 [80] **Location**: 18 centers in Israel **Sponsor:** Not stated	**Type of study:** Subgroup analysis of RCT **Blinding**: Un-blinded **Follow-up:** 3-years	**Inclusion criteria:** age 45-74, clinically established CAD based on a verified history of MI 6 months and 5 years prior to screening, and/or stable angina pectoris with symptoms present during 2 year preceding examination, and documentation of CAD **Exclusion criteria:** patients with insulin-dependent diabetes **Baseline data:** mean age 60±7, 2060 men, 663 women, more patients in the treatment group had hypertension, 77% in control group had prior MI, 73% in beta-blocker group had prior MI	**Groups:** C: 400 mg/day bezafibrate Rx: 400 mg/day bezafibrate plus propranolol or a cardioselective beta-blocker	**Initial N:** 3,122 (2723 had diabetes 19%) C: 1812 Rx: 911 **Final N:** Not stated	**Total mortality:** C: 14.9% Rx: 7.8% 44% risk reduction p<0.05 **Cardiac Mortality:** C: 8.4% Rx: 4.9% 42% reduction p<0.05	The evaluation was a subgroup analysis

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 18.5: Drug Therapy for Primary and Secondary Prevention of Cardiovascular Events in the General Diabetes Population *RCT*

Study, Total n	Treatment Groups Size & Drug	Study Population	Results	Comments
Gaede. 2003 [143] **(RCT)** **Follow-up**: 8 years **Initial N:** 160 **Final N:** 130	**Rx1** Intensive Treatment (n=80) Strict treatment goals Dietary intervention(low fat);light to moderate exercise recommended; invitation for smoking-cessation courses ACE-I-50 mg captopril bid or, if ACE-I contraindicated, ARB-50mg losartan bid Daily vitamin-mineral supplements Daily Aspirin (150mg) If HbA1c >6.5 at 3 months , metformin (max 1g bid) or gliclazide (max 160 bid) or combination. If HbA1c>7.0, NPH at bedtime. If still no decrease in HbA1c, regular and NPH insulin bid to qd. HTN: In addition to ACE-I prescribed for microalbuminuria, thiazide, calcium channel blockers, and beta-blockers added as needed. Atorvastatin (max: 80 mg daily) for raised serum cholesterol concentrations or combined dyslipidemia. Fibrates for hypertriglyceridemia (triglycerides >350 mg/dL) **Rx2** Conventional Treatment (n=80) Treated in accordance with national guidelines	Inclusion criteria: Patients from the Steno Diabetes Center Urine albumin excretion rates of 30-300 mg in a 24 h urine sample Exclusion criteria: Age >65, age<40 Stimulated C-peptide concentration <600pmol/L 6 min after IV injection of 1 mg glucagon Pancreatic insufficiency or diabetes secondary to pancreatitis Alcohol abuse Non-diabetic kidney disease Malignancy Life threatening disease with death probably in 4 years.	**Primary endpoint:** composite of death from CV causes, non fatal MI, CABG, percutaneous coronary intervention, nonfatal stroke, amputation as a result of ischemia, or vascular surgery for peripheral atherosclerotic artery disease Hazard ratio (95% CI) CV disease 0.47 (0.24-0.73) Nephropathy 0.39(0.17-0.87) Retinopathy 0.42 (0.21-0.86) Autonomic neuropathy 0.37 (0.18-0.79)	A focused, multifactorial intervention with continued patient education and motivation and strict targets and individualized risk assessment reduces composite CV outcomes in patients with type 2 diabetes and microalbuminuria. **Bias**: Small n Only composite CV endpoint reported Because of multiple components of intervention (diet, exercise, strict treatment goals, vitamin supplements, drug therapy etc.) , difficult to attribute any specific component (or combination of specific components) to positive outcomes May be difficult to replicate

Management of Blood Glucose

Problem Formulation 19

Clinical Question:	Should intensive (near normal) glucose control or conventional glucose control be used in people with diabetes?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 and type 2 diabetes.
Population:	All adults with known diabetes
Health Problem:	Abnormal blood glucose levels (complications related to poor glycemic control)
Health Intervention:	▪ Intensive glycemic control ▪ Conventional glycemic control ▪ No treatment ▪ All therapies were compared with each other, not in combination
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and registered nurses
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ MI ▪ Blindness ▪ Amputations ▪ Renal failure ▪ Neuropathy ▪ Weight ▪ Intermediate outcomes: ▪ Retinopathy, ▪ HbA1c
Side Effects of the Intervention:	▪ Diabetic coma ▪ Weight gain ▪ Decreased Quality of Life ▪ Seizure ▪ Increased intermediate outcome: hypoglycemia

Initial Drug Therapy for Glucose Lowering in Type 2 Diabetes

Problem Formulation 20

Clinical Question:	Which glucose lowering drug should be used as the first-line agent for people with type 2 diabetes?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 and 2 diabetes.
Population:	All adults with known diabetes
Health Problem:	Abnormal blood glucose levels (complications related to poor glycemic control)
Health Intervention:	▪ Insulin ▪ Sulphonylurea ▪ Metformin ▪ Pioglitazone ▪ Rosiglitazone ▪ No treatment ▪ Thiazolidinediones All therapies were compared with each other, not in combination.
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Weight loss ▪ Mortality ▪ MI ▪ Blindness ▪ Amputations ▪ Renal failure ▪ Intermediate outcomes: ▪ Development of or progression to retinopathy ▪ Neuropathy ▪ HbA1c ▪ Amputation
Side Effects of the Intervention:	▪ Diabetic coma ▪ Weight gain ▪ Decreased Quality of Life ▪ Seizure
Increased Intermediate Outcome:	▪ Hypoglycemia

Step Therapy for Glucose Control

Problem Formulation 21

Clinical Question:	When patients with diabetes cannot attain sufficient glucose control with first-line agents, what is the appropriate next step for therapy?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 and 2 diabetes.
Population:	All adults with known diabetes
Health Problem:	Abnormal blood glucose levels (complications related to poor glycemic control)
Health Intervention:	▪ Insulin ▪ Sulphonylurea ▪ Metformin ▪ Pioglitazone ▪ Rosiglitazone ▪ No treatment ▪ All therapies were compared with each other, not in combination ▪ Thiazolidinediones
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Weight loss ▪ Mortality ▪ MI ▪ Blindness ▪ Amputations ▪ Renal failure ▪ Intermediate outcomes: ▪ Development of or progression to retinopathy ▪ Neuropathy ▪ HbA1c ▪ Amputation
Side Effects of the Intervention:	▪ Diabetic coma ▪ Weight gain ▪ Decreased Quality of Life ▪ Seizure ▪ Increased intermediate outcome: hypoglycemia

Glycemic Control Target

Problem Formulation 22

Clinical Question:	What is the optimal HbA1c target for glucose-lowering therapy?	
Population:	All adults with known diabetes	
Health Intervention:	▪ Glycemic control to specific target ▪ Other target or no specific target	
Most Important Health Outcomes:	▪ Mortality ▪ MI ▪ Blindness	▪ Amputations ▪ Renal failure
Side Effects of the Intervention:	▪ Diabetic coma ▪ Weight gain ▪ Decreased quality of life ▪ Increased mortality ▪ Seizure ▪ Hypoglycemia ▪ Cardiovascular disease	
Intermediate Outcomes	▪ Development of or progression to retinopathy ▪ Neuropathy	▪ HbA1c ▪ Amputation ▪ Hypoglycemia

Microalbumin Assessments for Patients with Diabetes and Documented Microalbuminuria on ACE Inhibitors or ARBs

Problem Formulation 23A

Clinical Question:	At what HbA1c level should action be taken to lower blood glucose?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 and type 2 diabetes.
Population:	All adults with known diabetes
Health Problem:	Poor glycemic control and complications related to poor glycemic control
Health Intervention:	▪ Intensive HbA1c threshold and target ▪ No HbA1c threshold and target
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RN
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Mortality ▪ MI ▪ Blindness ▪ Amputations ▪ Renal failure
Side Effects of the Intervention:	▪ Diabetic coma ▪ Weight gain ▪ Decreased quality of life ▪ Increased mortality (combination metformin/sulphonylurea) ▪ Seizure ▪ Increased intermediate outcome: hypoglycemia
Intermediate Outcomes	▪ Development of or progression to retinopathy ▪ Neuropathy ▪ HbA1c ▪ Amputation ▪ Hypoglycemia

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MESH] ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND (("2007/08/08"[EDAT] : "2009/09/04"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/08/07 - 09/4/09	1/65
PubMed	glycemic control AND diabetes AND optimal hemoglobin a1c target (glycemic[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (optimal[All Fields] AND ("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR ("hemoglobin"[All Fields] AND "a1c"[All Fields]) OR "hemoglobin a1c"[All Fields]) AND target[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])	All Adult: 19+ years, English, Human	8/01/07 - 09/15/09	0/1

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	(HbA1c OR hemoglobin A1c) AND diabetes ((("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR "HbA1c"[All Fields]) OR ("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR ("hemoglobin"[All Fields] AND "a1c"[All Fields]) OR "hemoglobin a1c"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/01/07-09/15/09	1/12
PubMed	(HbA1c OR hemoglobin A1c) AND diabetes ((("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR "HbA1c"[All Fields]) OR ("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR ("hemoglobin"[All Fields] AND "a1c"[All Fields]) OR "hemoglobin a1c"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	RCT, All Adult: 19+ years, English, Human	8/01/07-09/15/09	0/340

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	(intensive[All Fields] AND ("glucose"[MeSH Terms] OR "glucose"[All Fields]) AND target[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	RCT, All Adult: 19+ years, English, Human	8/01/07-09/15/09	0/5
PubMed	(target[All Fields] OR optimal[All Fields]) AND (("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR "HbA1c"[All Fields]) OR ("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR ("hemoglobin"[All Fields] AND "a1c"[All Fields]) OR "hemoglobin a1c"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms])	RCT, All Adult: 19+ years, English, Human	8/01/07-09/15/09	0/43

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	(target[All Fields] OR optimal[All Fields]) AND (("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR "HbA1c"[All Fields]) OR ("hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR ("hemoglobin"[All Fields] AND "a1c"[All Fields]) OR "hemoglobin a1c"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Randomized Controlled Trial[ptyp] AND "adult"[MeSH Terms]) AND (("2007/08/01"[EDAT] : "2009/09/15"[EDAT]) AND "humans"[MeSH Terms] AND English[lang] AND Meta-Analysis[ptyp]] AND "adult"[MeSH Terms])	Meta-analysis, All Adult: 19+ years, English, Human	8/01/07-09/15/09	0/0
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05-09/4/09	0/67
Clinical Evidence	No terms used - searched book section Endocrine and Metabolic Disorders, Conditions: Diabetes, Pregnancy and Childbirth	Systematic reviews and RCTs	7/15/05-09/4/09	0/0
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/28/2007	4/132

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH] AND ("Blood Glucose"[MeSH] OR "Blood Glucose/drug effects"[MeSH]) AND ("Insulin"[Mesh] OR "Metformin"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR "Thiazolidinediones"[Mesh] OR "pioglitazone "[Substance Name] OR "rosiglitazone "[Substance Name])	Randomized, controlled trial, Meta-analysis, All Adult: 19+ years English, Human	7/2005 – 7/28/2007	1/245
PubMed	"Diabetes Mellitus"[MeSH] AND ("Blood Glucose"[MeSH] OR "Blood Glucose/drug effects"[MeSH])	Randomized, controlled trial, All Adult: 19+ years English, Human	8/01/03 – 7/15/05	0/384
PubMed	((((("Diabetes Mellitus"[MESH] AND ("blood glucose/drug effects"[MESH] OR "Hemoglobin A, Glycosylated"[MESH])) AND ((("metformin" [MeSH Terms] AND "insulin"[MeSH Terms]) OR ("metformin"[MeSH Terms] AND "Sulfonylurea Compounds" [MESH])) OR ("metformin"[MeSH Terms] AND pioglitazones[All Fields]))) AND Randomized, controlled trial[ptyp]) AND English[Lang]) AND "adult"[MeSH Terms]) AND "human"[MeSH Terms])	Randomized, controlled trial, All Adult: 19+ years English, Human	1/2001 – 3/2003	0/26
PubMed	((((("Diabetes Mellitus"[MESH] AND ("blood glucose/drug effects"[MESH] OR "Hemoglobin A, Glycosylated" [MESH])) AND ((("metformin"[MeSH Terms] AND "insulin"[MeSH Terms]) OR ("metformin"[MeSH Terms] AND "Sulfonylurea Compounds"[MESH])) OR ("metformin"[MeSH Terms] AND pioglitazones[All Fields]))) AND Randomized, controlled trial[ptyp]) AND English[Lang]) AND "adult"[MeSH Terms]) AND "human"[MeSH Terms])	Randomized, controlled trial, Adult, English, Human	07/01/00 – 12/20/01	0/6

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	6/18

Evidence Tables

Table 23.1: Effect of intensive (near normal) glucose control or conventional glucose control (systematic review)

Table Study, Total N	Study Population	Results		Comments
Glucose Control				
Stettler C, 2006 (meta-analysis) **# studies found: 125** **# studies included: 10** **Total N = 6272** Heterogeneity: Where heterogeneity suggested, random effect model was applied and indicated.	Randomized trials with parallel-group design of adult patients with DM 14 comparisons 8 studies of patients with type 1 DM 6 studies of patients with type 2 DM Mean baseline HbA1c Pre-treatment Type 1 DM 8.8% to 11.8% Type 2 DM 7.0% to 9.5% Post-treatment Type 1 DM -0.5% to -1.9% Type 2 DM -0.3% to -2.2%	**Outcomes of Interest:** **Incidence Rate Ratios** All events: Type 1: 0.38 (95% CI 0.26-0.56) Type 2: 0.81 (95% CI 0.73-0.91) P<0.001 Cardiac events Type 1: 0.41 (95% CI 0.19-0.87) Type 2: 0.91 (95% CI 0.80-1.03) P=0.040	Peripheral vascular events: Type 1: 0.39 (95% CI 0.25-0.62) Type 2: 0.58 (95% CI 0.38-0.89) P=0.22 Stroke Type 1: 0.34 (95% CI 0.05-2.57) Type 2: 0.58 (95% CI 0.46-0.74) P=0.54 Death: Type 1: 0.89 (95% CI 0.27-2.98) Type 2: 0.88 (95% CI 0.72-1.08)	Intensified treatment was associated with a reduced risk of macrovascular events in all groups. **Limitations**: No standard regimen was utilized for the treatment of either conventionally treated or intensively treated groups.

Table 23.2: First-Line Therapy (systematic reviews)

Study, Total N	Study Population Treatment Groups & Drug	Results	Comments
First-Line Therapy			
Richter, 2006 (Cochrane systematic review) **# studies found: 69** **# studies included: 22** **Total N 6200** Heterogeneity: Where heterogeneity was suggested, random effect model was applied and indicated.	Randomized trials with parallel-group design of adult patients with type 2 DM 16 studies of pioglitazone monotherapy 4 comparisons of pioglitazone with placebo 9 comparisons of pioglitazone with insulin secretogogues 1 comparison of pioglitazone with acarbose 1 comparison of pioglitazone with rosiglitazone 4 comparisons of pioglitazone with metformin Data from studies of pioglitazone monotherapy versus placebo were pooled for meta-analysis	**Outcomes of Interest:** Time from randomization to death from any cause, non-fatal MI, stroke, ACS, or surgery for pioglitazone versus placebo: HR 0.90 (95% CI 0.80 to 1.02, P=0.095) Time to the first event of death from any cause, MI, and stroke for pioglitazone versus placebo: HR 0.84 (95% CI 0.72 to 0.98, P=0.027). Reduction in HbA1c: Pioglitazone group 0,8% Placebo group 0.3%	**Reported conclusions:** Pioglitazone treatment does not positively influence mortality, morbidity, adverse effects, costs, or health-related quality of life. It did not demonstrate clinically relevant differences from other oral antidiabetic drugs. **Adverse effects:** The risk of edema was significantly greater for patients receiving pioglitazone. Odds ratio 2.86 (95% CI 2.14 to 3.18, P < 0.00001)
Richter, 2007 (Cochrane systematic review) **# studies found: 40** **# studies included: 18** Heterogeneity: Where heterogeneity was suggested, random effect model was applied and indicated.	Randomized trials with parallel-group design of adult patients with type 2 DM 10 studies of rosiglitazone monotherapy 5 comparisons of rosiglitazone with placebo 3 comparisons of rosiglitazone with metformin 2 comparisons of rosiglitazone with glyburide 1 comparison of rosiglitazone with repaglinide 1 comparison of rosiglitazone with pioglitazone	**Outcomes of Interest:** Data on the primary outcome of edema were suitable for pooling for meta-analysis. Edema was reported by a significantly larger proportion of patients on rosiglitazone than by patients in comparison groups Odds ratio 2.27 (95% CI 1.83 to 2.81, P < 0.00001).	**Reported conclusions:** Rosiglitazone treatment does not positively influence mortality, morbidity, adverse effects, costs, or health-related quality of life. It did not demonstrate clinically relevant differences from other oral antidiabetic drugs. The rate of edema was significantly increased. **Adverse effects:** Larger numbers of hospitalizations and cases of vascular disease were noted by the authors in the group treated with rosiglitazone, but data were not sufficient for statistical analysis

Table 23.3: Second-Line Therapy (Randomized Open-Label Trial)

Name	N	Mean ages	% female	Follow-up Rate	Follow-up Time	Baseline HbA1c%	FU HbA1c%	Effect Difference	p	Study quality†	Biases*
Yki-Jarvinen, 2006	Glargine 61 NPH 49	56±1 57±1	38 35	98.2%	36 weeks	9.13±0.15 9.26±0.15	7.14±0.12 7.16±0.14	NS		2	N

† Study quality measured by Jadad trials scoring system

* Biases: N: None; 1: Sample attrition >15%; 2: Sample selection bias; 3: Detection bias (e.g., measurement error, power); 4: Study Procedure biases

Table 23.4

Study	Inclusion & Exclusion Criteria	Age	Limitations/biases	Intervention & dose – N and Final N	Duration	Outcome	Relative Risk (RR) or Hazard Ratio(HR) 95% CI	NNT	p value
Glucose Control and CVD									
Selvin (2002) Meta Analysis	Prospective cohort studies with data on glycosylated hemoglobin levels and incident CV disease	N/A	Publication bias. Heterogeneity across studies. Small number of total trials included	3 studies for type 1 diabetes (n=1688) 10 studies for type 2 diabetes (n=7435)		Cardiovascular Disease For every one point increase in glycosylated hemoglobin –type 2 For every one point increase in glycosylated hemoglobin –type 2	1.18 (1.10-1.26) 1.15(0.92-1.43)		<.05 <.05
Pioglitazone, metformin, and glicazide – CV effects									
Belcher (2004) Meta Analysis	Trials in type 2 diabetes with either pioglitazone, metformin or sulfonylurea, gliclazide	N/A	No indication of systematic search strategy.	1. pioglitazone (up to 45 mg daily) 2. metformin (up to 2550 mg daily or a sulphonylurea 3. glicazide (up to 320 mg daily) 4 trials, N= 3700		Overall mortality Pioglitazone: 7/1857 Non pioglitazone: 10/1856 CHF Pioglitazone: 12/1857 Non-pioglitazone: 10/1856	- -	- -	NS NS

Table 23.5: Systematic Reviews- 2005 Search

Author & Title	Last Update & Search Database	Study Characteristics and Results (95% CI)	Reported Conclusions	Comments / Biases
Thiazolidinediones				
Noble J, et al (2005) Systematic Review	**LAST UPDATE:** 2005 **OBJECTIVE:** to review evidence supporting the use of thiazolidinediones (TZDs) in management of type 2 diabetes mellitus (DM2) **DATA SOURCES/SEARCH STRATEGY:** MEDLINE, Cochrane Database of Systematic Reviews. The RCTs reviewed were grouped into four areas: TZDs as monotherapy, TZDs compared with metformin, TZDs in combination with metformin, and TZDs in combination with sulfonylureas.	**CHARACTERISTICS OF THE SYSTEMATIC REVIEWS AND META-ANALYSES:** **Inclusion and exclusion criteria:** Description as a systematic review or meta-analysis, or a review article with a methods section or a clear description of the search strategy used to identify individual studies. Focused on the treatment of ADHD and, if it included studies of patients with other conditions, a separate analysis was reported. Published in a pee-reviewed journal.	"Most published systematic reviews and meta-analyses on the treatment of ADHD have limited value for guiding clinical, policy, and research decisions. A rigorous, systematic review following established methodological criteria is warranted"	

Table 23.6

Author & Title	Last Update & Search Database	Study Characteristics and Results (95% CI)	Reported Conclusions	Comments / Biases
Insulins				
Siebenhofer (2005) Systematic Review	**LAST UPDATE:** 5/19/2005 **OBJECTIVE:** to assess the effect of treatment with short acting insulin analogues vs. regular human insulin **DATA SOURCES/SEARCH STRATEGY:** Literature search using The Cochrane Library (issue 4, 2003), MEDLINE and EMBASE. Screening of abstracts of major diabetology meetings (European Association for the Study of Diabetes, American Diabetes Association) ongoing from 1992 and articles of diabetes journals (Diabetologia, Diabetic Medicine, Diabetes Care, Diabetes) until December 2003.	**CHARACTERISTICS OF THE SYSTEMATIC REVIEWS AND META-ANALYSES:** **Inclusion and exclusion criteria:** All randomised controlled trials (blinded and open, parallel and cross-over design) with a treatment duration of four weeks or more, designed to compare diabetic patients who were treated with the currently on the market available short acting insulin analogues Lispro or Aspart vs. regular human insulin were included in the review, regardless of dose or schedule, if insulin was injected subcutaneously via syringe, pen or pump. **INTERVENTIONS and RESULTS:** 42 RCTs were determined to be potentially appropriate for inclusion in the meta-analysis Altogether 7933 participants took part in the 42 randomised controlled studies. 5925 type 1 diabetic patients, 1901 type 2 diabetic patients and 107 women with gestational diabetes were investigated. The weighted mean age of adult type 1 diabetic participants in the parallel trials was 37.4 vs. 37.1 years for analogue vs. regular insulin, the diabetes duration 14.7 vs. 14.5 years, and the body mass index 25.0 vs. 24.8 kg/m2. Type 1 diabetic participants of crossover studies were slightly younger (35.3 years), had shorter diabetes duration (13.6 years) and a body mass index of 24.5 kg/m2. The weighted mean age of type 2 diabetic participants in the parallel trials was 56.8 vs. 56.7 years for analogue vs. regular insulin, the diabetes duration 11.9 vs. 11.7 years, and the body mass index 28.2 vs. 28.1 kg/m2. Type 2 diabetic participants of crossover studies had a mean age of 58.3 years, a diabetes duration of 12.4 years and a body mass index of 28.8 kg/m2.	"Our analysis suggests only a minor clinical benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long-term efficacy and safety data are available, we suggest a cautious response to the vigorous promotion of insulin analogues."	
Goudswaard (2005) Systematic Review	**LAST UPDATE:** 5/25/2005 **OBJECTIVE:** To assess the effects of insulin monotherapy vs. insulin-oral hypoglycaemic agents combination therapy. **DATA SOURCES/SEARCH STRATEGY:** The Cochrane Library (issue 2, 2004; including the Cochrane Controlled Trials Register (CCTR) and the Database of Reviews of Effectiveness (DARE), MEDLINE (1966 to 05/2004), EMBASE (1974 to 05/2004), Current Controlled Trials (www.controlled-trials.com); The National Research Register	**CHARACTERISTICS OF THE SYSTEMATIC REVIEWS AND META-ANALYSES:** **Inclusion and exclusion criteria:** Randomised controlled trials (RCTs of any design) with a minimum follow-up duration of two months. MAIN OUTCOME MEASURES 1. Any diabetes-related morbidity: myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction; 2. Glycaemic control (fasting blood glucose, HbA1, HbA1c). **INTERVENTIONS and RESULTS:** 20 RCTs were determined to be potentially appropriate for inclusion in the meta-analysis All 20 included studies were randomised controlled studies, of which 16 had a parallel design, and four a crossover design. Weighted mean trial duration was 10.0 months (range 2 to 36 months). A total of 1811 participants (mean per study 91; range 10 to 432) were included in these studies, with 46% men (range 29% to 64%). Participants had mean age of 59.8 years (95% CI 57.6 to 62.1), and mean known duration of diabetes was 9.6 years (95% CI 8.3 to 10.9). All studies provided information on oral hypoglycaemic therapy at baseline.	Bedtime NPH insulin combined with oral hypoglycaemic agents provides comparable glycaemic control to insulin monotherapy and is associated with less weight gain if metformin is used.	

Table 23.7: Conventional vs. Intensive Blood Glucose Lowering Therapy in Type 1 and Type 2 Diabetes on Microvascular and Neuropathic Complications

Summary of Meta-Analysis from Clinical Evidence

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval) All results in favor of intensive therapy	Adverse Effects	Conclusions
Herman, WH. **Glycaemic control in diabetes.** Clinical Evidence 2001;403-411 (89) **References of studies included in the systematic review:** Wang PH, Meta-analysis of effects of intensive blood glucose control on late complications of type 1 diabetes. Lancet 1993;341:1306-1309 (93) The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986 (84) Ohkubo Y, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-117 (91) 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. Lancet. 1998;352:837-53 (85)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** not stated	**Number of studies included:** 1 Systematic Review (16 small RCTs with type 1 diabetes), 3 additional RCTs **Intervention:** sulphonylurea insulin diet therapy **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 1441-3867 **Duration of Trials:** 8 months - 10 years	**Inclusion criteria:** Type 1 and 2 diabetes In one study half had mild retinopathy and the other had no retinopathy In one study patients had newly diagnosed type 2 diabetes, fasting plasma glucose 6.1-15.0 mmol/l after 3 months dietary therapy, no symptoms of hyperglycemia **Age Range:** 25-65	**Progression of retinopathy:** OR 0.49 (0.28, 0.85); 0.39 (0.28, 0.55) type 1 OR 0.25 (0.09, 0.65); 0.66 (0.48, 0.92) type 2 NNT 5(4,7) over 6.5 years in type 1 NNT 4(3, 11) over 6 years, 10(6,50) over 10 years in type 2 **Development of retinopathy:** OR 0.22 (0.14, 0.36) type 1 NNT 6 (5, 7) over 6.5 years in type 1 **Progression or development of nephropathy:** OR 0.34 (0.20, 0.58); 0.50 (0.39, 0.63) type 1 OR 0.26 (0.09, 0.76); 0.54 (0.25, 1.18) type 2 NNT 7(6, 11) over 6.5 years in type 1 NNT 5 (4, 19) over 6 years in type 2 **Development of neuropathy:** OR 0.36 (0.24, 0.54) type 1 OR 0.42 (0.23, 0.78) type 2 NNT 13 (11, 18) over 6.5 years in type 1 NNT 5 (3, 16) over 10 years in type 2 **Diabetes-related end points (sudden death, hyperglycemia, hypoglycemia, fatal/non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in 1-eye, or cataract extraction):** 40.9 vs. 46.0 events/1000 person years ;RRR 12% (1%, 21%) type 2 **Diabetes related deaths:** 10.4 vs. 11.5 deaths/1000 person years ; RRR 10% (-11%, 27%) type 2 **All causes of mortality:** 17.9 vs. 18.9 deaths/1000 person years; RRR 6% (-10%, 20%) type 2 **Microvascular end points:** 8.6 vs. 11.4/1000 person years; RRR 25% (7%, 40%) type 2 **Change in HbA1c:** Range from 0.9% to 2.0% (type 2)	See additional adverse effects evidence table	There is strong evidence that intensive treatment reduces the development and progression of microvascular and neuropathic complications in both type 1 and type 2

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 23.8: Conventional vs. Intensive Blood Glucose Lowering Therapy in Type 1 and Type 2 Diabetes on Cardiovascular Outcomes

Summary of Meta-Analysis from Clinical Evidence

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)	Adverse Effects	Conclusions
Herman, WH. **Glycaemic control in diabetes.** Clinical Evidence 2001;403-411 (89) **References of studies included in the systematic review:** Lawson ML, et al. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. Diabetes Care. 1999;22 Suppl 2:B35-B39 (90) 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. Lancet. 1998;352:837-53 (85) Ohkubo Y, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-117 (91)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** not stated	**Number of studies included:** 1 systematic review (6 RCTs) and 2 RCTs **Intervention:** intensive insulin treatment diet therapy sulphonylurea **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 1731 patients (type 1) **Duration of Trials:** 2-10 years	**Inclusion criteria:** The systematic review only included patients with type 1 diabetes The other two RCTs included patients with type 2 diabetes In one study patients had newly diagnosed type 2 diabetes, fasting plasma glucose 6.1-15.0 mmol/l after 3 months dietary therapy, no symptoms of hyperglycemia **Age Range:** 25-65	**Absolute risk of MI (type 2):** Intensive therapy 14% Conventional therapy 16% RRR +13% (-2, 27) **Absolute risk of stroke (type 2):** Intensive therapy 5.4% Conventional therapy 4.8% RRI -12% (-17, 51) **Amputation or death from peripheral vascular disease:** Intensive therapy 1.1% Conventional therapy 1.6% RRR 33% (-20, 63) **Major cerebrovascular, cardiovascular and peripheral vascular events (type 2):** Intensive therapy 0.6/100 person years Conventional therapy 1.3/100 person years (small trial so results not statistically significant) **# Macrovascular events (type 1):** Intensive therapy OR 0.55 (0.35, 0.88) **# People developing macrovascular disease (type 1):** Intensive therapy OR 0.72 (0.44, 1.17) **Macrovascular mortality (type 1)** Intensive therapy OR 0.91 (0.31, 2.65)	See additional adverse effects evidence table	Intensive treatment is associated with a small but statistically insignificant reduction in cardiovascular risk There is no evidence that intensive treatment increases incidence of cardiovascular outcomes

Table 23.9: Effect of Blood Glucose Control on Cardiovascular Disease in Diabetics (Primary Prevention)

Summary of a Meta-Analysis from Clinical Evidence

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)	Adverse Effects	Conclusions
Sigal R and Malcolm J. **Cardiovascular disease in diabetes.** Clinical Evidence 2001;376-96 (33) **References of studies included in systematic review:** 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. Lancet. 1998;352:837-53 (85) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65 (86) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86 (84) Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol. 1995;75(14):894-903 (35)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Diabetes mellitus AND (Cardiovascular diseases OR Coronary disease OR Atherosclerosis OR Heart diseases OR Myocardial infarction OR Heart failure, congestive OR (coronary thrombosis or exp death, sudden, cardiac) OR Hypertension OR Cerebrovascular disorders) AND ((Mass screening OR Smoking cessation OR Antihypertensive agents OR (antilipemic agents/ or exp hydroxymethylglutaryl-coa reductase inhibitors) OR (lipid lower* agents) OR Gemfibrozil OR Aspirin OR Hypoglycemic agents)) OR (((Blood glucose AND (lower* OR control*)) OR ((glycaemic or glycemic) and control*))) AND ((Proteinuria AND (treat* or reduc*)) OR (angioplasty OR angioplasty, transluminal, percutaneous coronary) OR Stents OR Coronary artery bypass OR Myocardial revascularization OR Platelet glycoprotein gpiib-iiia complex OR abciximab))	**Number of studies included**: 2 RCTs **Intervention:** Conventional treatment vs. intensive insulin therapy (type 1) Conventional treatment vs. intensive insulin and/or sulphonylurea therapy (type 2) For people ≥120% over ideal body weight conventional treatment vs. intensive insulin, metformin, sulphonylurea (type 2) **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 1441 (type 1) 3867 (type 2) **Duration of Trials:** 6.5 years (type 1) 5 years (type 2)	**Inclusion criteria:** Type 1: no baseline cardiovascular disease, hypertension, hypercholesterolemia, nor obesity Type 2: Uncontrolled DM on diet therapy only without cardiovascular disease **Age Range:** 13-39 (type 1) 25-65 (type 2)	**Macrovascular Events (combined fatal or non-fatal MI, sudden cardiac death, revascularization procedure, angina with CAD, stroke, lower limb amputation, peripheral vascular disease) (type 1):** Conventional 40 (5.5%) Intensive (insulin) 23 (3.2%) ARR 2.2%; RR 0.09 (0.32, 1.1) p=ns; NNT 16 (10, 71) over 5 years **Diabetes Related Death (type2)** RR 0.58 (0.37, 0.91) (metformin) NNT 19 **Absolute Risk of AMI (type 2):** Conventional 17.4/1000 person years Intensive (insulin and or sulphonylurea, or metformin) 14.7/1000 person years RR 0.84 (0.71, 1.0) **MI (fatal or non-fatal events for type 2)** Conventional 14.2% Intensive (insulin and or sulphonylurea) 16.3% NNT 46 **MI (fatal or non-fatal events for type 2)** Conventional 11% Intensive (metformin) 18% NNT 16 (10, 71) **Improvement in HbA1c (type 2):** Conventional 7.9% Intensive (insulin, sulphonylurea, or metformin) 7.0% **Diabetes-related endpoints (sudden death, hyperglycemia, hypoglycemia, fatal/non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in 1-eye, or cataract extraction) (type 2):** RR 0.88 (0.80, 0.99) (insulin, sulphonylurea, or metformin) NNT 39 for 5 years to prevent 1 additional DM endpoint Risk Reduction of 32% (13, 47) (metformin) P=0.002	Increased incidence of hypoglycemia with sulphonylureas and insulin, especially intensive therapy in type 1 patients Increased risk of weight gain with insulin and sulphonylureas No evidence that a specific treatment increases overall risk of cardiovascular disease	Intensive glycemic control reduces microvascular disease but the role is unclear in primary prevention of cardiovascular events Type 1: Young participant age and low cardiovascular events limits the power of the study to detect the effect of intensive treatment Type 2:The effect of tighter glycemic control was limited by the small achievement in HbA1c improvement Since intensive glucose control with metformin appears to decrease the risk of diabetes-related end points (including all cause mortality, stroke and any diabetes-related end point) and is associated with less weight gain and fewer hypoglycemic attacks than with insulin and sulphonylurea. Metformin may be the first-line drug therapy of choice in overweight, middle-aged patients who have type 2 diabetes.

Table 23.10: Effect of Blood Glucose Control on Cardiovascular Disease in Type 2 Diabetes (Secondary Prevention-VA study)

Summary of RCTs Included in Clinical Evidence

Study Name	Design	Population	Treatment Groups	Size	Results (95% CI)	Bias
Abraira C, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes. Arch Intern Med 1997; 157:181-188 [92] Location: US	Type of study: RCT Blinding: double-blind Follow-up: 27 months	Inclusion criteria: males, age 40-69 yr, treated at entry with a maximum dose of sulphonylurea or with insulin, exhibiting an HbA1c level >3 SDs above the normal mean (5.05 + 3 x 0.50 = > 6.55%), preexisting nonincapacitating cardiovascular disease Exclusion criteria: more than 1 preexisting myocardial infarction, severe congestive heart failure (New York Heart Association class III or IV), amputation due to gangrene, elevated serum creatinine levels >141.4 micromoles/L [>1.6 mg/dl]), albuminuria over 500 mg/dl, or symptomatic neuropathy Baseline data: men with a mean age of 60±6 years and diagnosis of NIDDM for 7.8±4.0 years	Groups: C: injected insulin once daily Rx: a stepped therapy designed to attain near-normal glycemic levels was used (Regimen began with 1 injection of insulin in the evening (phase I). If the glycemic goal was not met, each patient successively received more intensive therapy, consisting of an evening insulin injection with daytime glipizide (phase II), 2 injections of insulin alone (phase III), or 3 or more injections of insulin (phase IV))	Initial N: C: 78 Rx: 75 Final N: Only one patient withdrew Compliance: Not stated	New cardiovascular events (including MI stroke, CHF, amputation, CV mortality, angina or CVD, antioplasty or bypass graft surgery, ischemic attacks, new claudication, or ischemic ulcers): C: 16 (20%) Rx: 24 (32%) RR 1.6 (0.92, 2.5) p=0.10 Mean HbA1c: After 6 months, the mean HbA1c level in the intensive treatment arm was 7.1%, and remained 2.1% lower than in the standard treatment arm for the duration of the trial (P<0.001) Adverse Events: Severe hypoglycemia was rare (2 events per 100 patients per year) and not significantly different between arms. Mild (84%) and moderate (16%) hypoglycemic events occurred more frequently in the intensive treatment arm (16.5 per patient per year) than in the standard treatment arm (1.5 per patient per year [p<0.001]).	Only included men

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 23.11: Adverse Effects of Conventional vs. Intensive Blood Glucose Lowering Therapy in Type 1 and Type 2 Diabetes

Summary of Meta-Analysis from Clinical Evidence

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)		Quality of Life	Conclusions
Herman, WH. **Glycaemic control in diabetes.** Clinical Evidence 2001;403-411 (89)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** not stated	**Number of studies included:** Hypoglycemia – 1 systematic review and (type 1) and 3 RCTs (type 2) Weight gain – 4 RCTs (both type 1 and type 2) 1 systematic review Quality of Life – 3 RCTs **Intervention:** intensive insulin treatment diet therapy sulphonylurea metformin **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 110-3867 (type 2); 2067 (type 1) **Duration of Trials:** 0.5-10 years	**Inclusion criteria:** Patients with both type 1 and 2 diabetes **Age Range:** not stated	**Incidence of Severe Hypoglycemia (type 1):** intensive therapy 7.9 episodes/100 person years conventional therapy 4.6 episodes/100 person years OR 3.0 (2.5, 3.6) Risk associated with degree of HbA1c lowering in intensive group (p=0.005) **Rates of major hypoglycemia (type 2):** conventional therapy 0.7% chlorpropamide 1.0% glibenclamide 1.4% insulin 1.8% (p<0.0001 for intensive therapy vs. conventional therapy) **Occurrences of major hypoglycemic episodes (type 2):** Metformin 0.6% in overweight people **Weight gain:** BMI increased by 5.8% in intervention group (p<0.01) type 1	Intensive therapy increase from 20.5 kg/m^2 to 21.2 kg/m^2 (type 2) Conventional therapy increase from 20.3 kg/m^2 to 21. kg/m^2 (type 2) p=ns mean 2.9 kg increase in intensive treatment group (type 2) p<0.001 4.0 kg insulin group, 2.6 kg chlorpropamide, 1.7 kg glibenclamide (type 2) metformin decreased weight and sulphonylurea increased weight difference 2.9 kg (1.1, 4.4) Risk of developing a body weight of 120% above ideal: Intensive therapy 12.7 cases/100 person years (gained 4.6 kg more than conventional therapy group at 5 yrs) Conventional therapy 9.3 cases/100 person years RR 1.33	Quality of life is lowered by complications – not directly by intensive vs. conventional therapy Intensive therapy did not reduce quality of life (type 1) Severe hypoglycemia was not consistently associated with a subsequent increase in distress or decline in quality of life Repeated severe hypoglycemic (≥3 events resulting in coma or seizure) increased distress Behavioral intervention plus intensive therapy significantly improved quality of life, diabetes and medical self-efficacy, and HbA1c (7.5% vs. 8.5%, p=0.001)	Intensive treatment is associated with hypoglycemia and weight gain without adverse impact on quality of life Diabetic complications increase with HbA1c concentrations above the non-diabetic range

Note: Comparisons that are not stated in the results column were not disclosed by the author.

References of studies included in the systematic review of adverse effects of intensive vs. conventional therapy:

Hypoglycemia
Egger M, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Diabet med 1997; 14:919-928.
UK Prospective Diabetes Study Group. Intensive blood-glucose with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352:837-852.
Ohkubo Y, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28:103-117.
UK Prospective Diabetes Study Group. Intensive blood-glucose with metformin on complications in overweight patients with type 2 diabetes. Lancet 1998; 352:854-865.
Weight Gain
The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977-986.
Ohkubo Y, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-117
UK Prospective Diabetes Study Group. Intensive blood-glucose with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352:837-852.
Reichard P, et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm diabetes intervention study (SDIS) after 5 years. J Intern Med 1991; 30:101-108.
Johansen K. Efficacy of metformin in the treatment of NIDDM. Diabetes Care 1999; 22:33-37.
Quality of Life
The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. Diabetes Care 1996; 19:195-203.
Grey M, et al. Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. J Pediatr 2000; 137:107-113.
UK Prospective Diabetes Study Group. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999; 22:1125-1136.

Table 23.12: Glycemic Control Target in Type 1 and Type 2 Diabetes

Summary of Meta-Analysis from Clinical Evidence

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Herman, WH. **Glycaemic control in diabetes.** Clinical Evidence 2001;403-411 [89] **References of studies included in the systematic review:** The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986 [84] 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. Lancet. 1998;352:837-53 [85]	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** not stated	**Number of studies included:** 2 RCTs **Intervention:** sulphonylurea insulin diet therapy metformin **Settings:** not stated **Heterogeneity:** not stated **Sample size range:** 1441-3642 **Duration of Trials:** not stated	**Inclusion criteria:** One study included at type 1 diabetics, the other included type 2 diabetics **Age Range:** not stated	**Each 1% decrease in mean HbA1c was associated with reduced risk of:** Any diabetes related microvascular or macrovascular event: RR 0.79 (0.79, 0.83) Diabetes related death: RR 0.79 (0.73, 0.83) All causes of mortality: RR 0.86 (0.81, 0.91) Microvascular complications: RR 0.63 (0.59, 0.67) MI: RR 0.86 (0.79, 0.92)	Both RCTs found hypoglycemia was increased by intensive treatment	Lower HbA1c was associated with a lower risk of complications As concentrations of HbA1c were reduced, the risk of complications fell but the risk of hypoglycemia increased Prospective observational data suggests that there is no lower glycemic threshold for the risk of complications; the better the glycemic control, the lower the risk of complications The rate of increase of risk for microvascular disease with hyperglycemia is greater than for macrovascular disease Intensive treatment in type 1 diabetes may not be favorable in older adults (age 65 or over) and in people with repeated severe hypoglycemia or who are unaware of hypoglycemia Intensive treatment in type 2 diabetes may be less favorable in older adults (age 65 or over) or in those with longstanding diabetes The benefits of intensive treatment is limited by the complications of advanced diabetes (blindness, ESRD or CVD), major comorbidity, and reduced life expectancy Risk of intensive treatment is increased by history of severe hypoglycemia or unawareness of hypoglycemia, advanced autonomic neuropathy, or CVD, and impaired ability to detect/treat hypoglycemia It may be appropriate to target a less intensive goal for people who may have limited benefit or increased risk with intensive treatment (reflect a persons self determined goals of care and willingness to make lifestyle modifications)

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 23.13: Summary of 2009 Search

Name Design	N	Mean HbA1c before intervention	Intensive Treatment Goal	Mean Duration of Intervention	Biases*	Results
Kelly et al. 2009 Meta-Analysis	28,000 5 studies **UKPDS 33, 1998** 3,867 **UKPDS 34, 1998** 753 **ACCORD, 2008** 10,251 **ADVANCE, 2008** 11,140 **VADT, 2009** 1,791	**UKPDS 33, 1998** Control: 6.9 Treatment: 7.0 **UKPDS 34, 1998** Control: 7.0 Treatment: 7.0 **ACCORD, 2008** Control: 8.1 Treatment:8.1 **ADVANCE, 2008** Control: 7.2 Treatment: 7.2 **VADT, 2009** Control: 9.4 Treatment: 9.4	**UKPDS 33, 1998** FPG <6.0 mmol/L **UKPDS 34, 1998** FPG <6.0 mmol/L **ACCORD, 2008** HbA1c<6.0% **ADVANCE, 2008** HbA1c≤6.5% **VADT, 2009** HbA1c<6.0%	**UKPDS 33, 1998** 10.0 yrs **UKPDS 34, 1998** 10.7 yrs **ACCORD, 2008** 3.4 yrs **ADVANCE, 2008** 5.0 yrs **VADT, 2009** 5.6 yrs	2,5	**Effect of Intensive Glucose Control on Most Important Health Outcomes** *(See body of rationale for tables and figures identifying other results.)* *All pooled risk below is per 1000 patients over 5 years of treatment.* **HbA1c levels:** • Intensive glucose control treatment goal for UKPDS 33, UKPDS 34, ACCORD, VADT: HbA1c <6.0 mmol/L • Intensive glucose control treatment goal for ADVANCE: HbA1c ≤6.5 mmol/L • All trials showed a greater decrease in the HbA1c levels in the intensive glucose control. • Mean difference range: -0.5% to -1.4% • Sample-size overall difference in median HbA1c: -0.8% **Pooled Risk for CVD:** • Relative Risk: 0.90 [95% CI 0.83-0.98] • Risk difference: -15 [95% CI -24 to -5] **Pooled Risk for CHD:** • Relative Risk: 0.89 [95% CI 0.81-0.96] • Risk difference: -11 [95% CI -17 to -5] **Pooled Risk for Cardiovascular Mortality:** • Relative Risk: 0.97 [95% CI 0.76-1.24] • Risk difference: -3 [95% CI -14 to7] **Pooled Risk for All-Cause Mortality:** • Relative Risk: 0.98 [95% CI 0.84-1.15] • Risk difference: -4 [95% CI -17 to 10] • There was notable trial heterogeneity for all-cause mortality finding. P for heterogeneity between the results of subgroup analyses is 0.095 for relative risk and 0.015 for risk difference. **Pooled Risk for Nonfatal Myocardial Infarction:** • Relative Risk: 0.84 [95% CI 0.75-0.94] • Risk difference: -9 [95% CI -16 to 3] **Pooled Risk for Fatal Myocardial Infarction:** • Relative Risk: 0.94 [95% CI 0.75-1.18] • Risk difference: -3 [95% CI -10 to 4] **Pooled Risk for Severe Hypoglycemia:** • Relative Risk: 2.03 [95% CI 1.46-2.81] • Risk difference: 39 [95% CI 7 to 71]

Monitoring Microalbumin in Patients with Diabetes and Documented Microalbuminuria on ACE Inhibitors

Problem Formulation 23B

Clinical Question:	Should repeat microalbumin measures be performed on patients with diabetes and documented microalbuminuria who are on an ACE inhibitor?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in understanding on whom and when to repeat microalbumin assessments.
Population:	Adults with type 1 and 2 diabetes with documented microalbuminuria who are on an ACE inhibitor
Health Problem:	Microalbuminuria (risk of end-stage renal disease - ESRD)
Health Intervention:	▪ Repeat measurement of microalbumin levels ▪ No monitoring
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, RNs, registered dieticians, and health educators
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ ESRD ▪ Cardiovascular events ▪ Dialysis
Side Effects of the Intervention:	▪ Inconvenience ▪ Anxiety due to the test ▪ Inaccurate test results
Intermediate Outcomes	▪ Albuminuria

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 08/2007	0/116
PubMed	"Diabetic Nephropathies /drug therapy"[MeSH] AND "Albuminuria/drug therapy"[MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	8/01/03 – 08/2007	0/59
	"Diabetic Nephropathies /drug therapy"[MeSH] AND "Albuminuria/drug therapy"[MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	2001 – 07/01/03	0/6
	"Diabetic Nephropathies /drug therapy"[MeSH] AND "Albuminuria/drug therapy"[MeSH] AND "Angiotensin-Converting Enzyme Inhibitors" [MeSH] AND “hypertension”[MESH]	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 07/10/01	0/33
Cochrane	Diabetes	Systematic reviews	7/15/05	0/47
Clinical Evidence	Diabetes	Systematic reviews and RCTs	7/15/05	0/0

Retinal Screening

Problem Formulation 24

Clinical Question:	Is there evidence to suggest a screening interval for diabetes patients, with or without documented background retinopathy?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals on who, when, and how to screen for diabetic retinopathy
Population:	Adults with type 1 and 2 diabetes
Health Problem:	Diabetic retinopathy
Health Intervention:	▪ Retinal screening ▪ No intervention
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Retinopathy ▪ Macular edema
Side Effects of the Intervention:	▪ Anxiety ▪ Inconvenience ▪ Inaccurate test results

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 08/2007	0/129
	"Mass Screening"[MeSH] AND "diabetic retinopathy" [MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 08/2007	0/12
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Evidence Tables

Table 24.1: Retinal Screening in Younger People with Diabetes who Use Insulin

Summary of a Prospective Cohort Study

Study Name	Design	Population	Groups	Size	Results	Bias
Klein R, et al. The Wisconsin Epidemiological Study of Diabetes Retinopathy. IX Four-year incidence and progression of diabetic retinopathy when age at diagnosis is < 30 years. Arch Opthalmol 1989;107(2):237-43 (112) Location: US Sponsor: National Eye Institute	Type of study: Prospective Cohort Blinding: N/A Follow-up: 4 years	Inclusion criteria: insulin-taking diabetics diagnosed before age 30 identified from primary care records as having diabetes Exclusion criteria: gestational diabetes, moved away from area, died between initial examination and assessment, confined to a nursing home Baseline data: 82% participated in baseline examination, 271 had no retinopathy in either eye, 20% had proliferate diabetic retinopathy, mean age 28 years, mean duration of diabetes 14 years, mean HbA1c 12.5%	Participants: Young insulin taking diabetics Exposure/Intervention: Ocular and physical exam (slit lamp, stereoscopic fundus photos of 7 standard fields) Detailed grading (field-by-field, lesion-by-lesion) and computer analyzed grade to derive a general retinopathy level Grade 10: No retinopathy Grade 21: Microaneurysms only, blot hemorrhages, or soft exudates in the absence of microaneurysms Grade 31: Microaneurysms and other retinal lesions	Initial N: 996 Final N: 891 were followed up completely	Patients without retinopathy at baseline who developed retinopathy at 4 years: 160 (59%) 34% (55/160) microaneurysms in 1 eye 3.8% (6/160) blot hemorrhages only 33.8% (54/160) microaneurysms one in both eyes 28.1% (45/160) microaneurysms and lesions Improvement of retinopathy in patients with baseline retinopathy: 7% of the population Patients without proliferate retinopathy at baseline who developed proliferate diabetic retinopathy: 75 (11%) Worsening of retinopathy in patients with less severe retinopathy: 41% of the population Progression to proliferate diabetic retinopathy: grade 10/10 at baseline 1/271 (0.4%) grade 21/<21 at baseline 20/66 (3.0%) grade 21/21 at baseline 5/105 (4.8%) grade 31/<31 at baseline 6/58 (10.3%) grade 31/31 at baseline 15/74 (20.3%) Progression to proliferate diabetic retinopathy with high-risk characteristics for severe visual loss: grade 10/10 at baseline 0/271 (0%) grade 21/<21 at baseline 1/66 (1.5%) grade 21/21 at baseline 0/105 (0%) grade 31/<31 at baseline 4/58 (6.9%) grade 31/31 at baseline 4/74 (5.4%)	Grading of photos is up to interpretation of the expert

Table 24.2: Retinal Screening in Older Patients with Diabetes Who Use and Do Not Use Insulin

Summary of a Prospective Cohort Study

Study Name	Design	Population	Groups	Size	Results	Bias
Klein R, et al. The Wisconsin Epidemiological Study of Diabetes Retinopathy: X Four-year incidence and progression of diabetic retinopathy when age at diagnosis 30 years or more. Arch Opthalmol 1989;107(2):244-9 (113) Location: US Sponsor: National Eye Institute	Type of study: Prospective Cohort 4 year incidence of macular edema and relationship to various risk factors Blinding: N/A Follow-up: 4 years	Inclusion criteria: diabetics diagnosed at age 30 or older identified from primary care records as having diabetes Exclusion criteria: gestational diabetes, moved away from area, died between initial examination and assessment, confined to a nursing home Baseline data Rx1: 77% participated in baseline examination, 32% had no retinopathy in either eye, 12% had proliferate diabetic retinopathy mean age 63 years, mean duration of diabetes 14 years, 45% men, mean HbA1c 11.8% Baseline data Rx2: 77% participated in baseline examination, 64% had no retinopathy in either eye, 2% had proliferate diabetic retinopathy mean age 66 years, mean duration of diabetes 8 years, 45% men, mean HbA1c 10.2%	Groups: Rx1: insulin users Rx2: non insulin users Examination: Ocular and physical exam (slit lamp, stereoscopic fundus photos of 7 standard fields)	Initial N: 1780 Final N/ Compliance: 96% were followed up completely	Patients without retinopathy at baseline who developed retinopathy at 4 years: Rx1 73/154 (47%) Rx2 110/320 (34%) Patients without proliferate retinopathy at baseline who developed proliferate diabetic retinopathy: Rx1 31/418 (7%) Rx2 11/486 (2%) Worsening of retinopathy: Rx1 142/418 (34%) Rx2 121/486 (25%) Progression to proliferate diabetic retinopathy (in worst eye): No retinopathy (grade 10) 2/474 (0.4%) Microaneurysms only, blot hemorrhages, or soft exudates in the absence of microaneurysms (grade 21) 1/161 (0.6%) Microaneurysms and other retinal lesions (grade 31-51) 67/269 (24%)	Grading of photos is up to interpretation of the expert

Table 24.3: Retinal Screening in Patients with Type 1 and 2 Diabetes Older and Younger than Age 30 Summary of a Prospective Cohort Study

Study Name	Design	Population	Groups	Size	Results	Bias
Klein R, et al. **The Wisconsin Epidemiological Study of Diabetes Retinopathy: XI The incidence of macular edema**. Opthalmol 1989;96:1501-10 (114) **Location:** US **Sponsor:** National Eye Institute	**Type of study:** Prospective Cohort 4 year incidence of macular edema and relationship to various risk factors **Blinding:** N/A **Follow-up:** 4 years	**Inclusion criteria:** identified from primary care records as having diabetes **Exclusion criteria:** gestational diabetes, moved away from area, died between initial examination and assessment, confined to a nursing home **Baseline data:** combination of Wisconsin IX and X	**Groups:** Rx1: younger insulin taking diabetics Rx2: older onset diabetics **Examination:** Ocular and physical exam (slit lamp, stereoscopic fundus photos of 7 standard fields)	**Initial N:** Rx1: 610 Rx2: 652 **Final N/ Compliance:** 96% were followed up completely	**Incidence of macular edema*** Rx1 50/610 (8.2%) Rx2 insulin users: 23/273 (8.4%) non-insulin users: 11/379 (2.9%) Incidence associated with higher HbA1c levels, long duration of diabetes, and more severe retinopathy at baseline *Macular edema was defined as thickening of the retina with or without partial loss of transparency within 1 DD of the center of the macula **Proportion of cases of macular edema that were clinically significant****: Rx1 26/52 (52%) Rx2: 19/34 (56%) **Clinically significant macular edema is defined as retinal thickening or hard exudates with thickening of the adjacent retina within 0.5mm of the center of the macula or zone of retinal thickening one disc area or larger located within one disc diameter of the center of the macula. **Progression to macular edema (worst eye):** No retinopathy (grade 10) Rx1 3/286 (1.0%) Rx2 5/450 (1.1%) Microaneurysms only, blot hemorrhages, or soft exudates in the absence of microaneurysms (grade 21) Rx1 15/150 (10%) Rx2 6/100 (6%) Microaneurysms and other retinal lesions (grade 31-51) Rx1 29/158 (18%) Rx2 21/98 (21%)	Grading of photos is up to interpretation of the expert

Foot Screening

Problem Formulation 25

Clinical Question:	Can patients at a high risk for foot disease be identified?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals on who, when, and how regarding foot monitoring for people with diabetes
Population:	Adults with type 1 and 2 diabetes
Health Problem:	Amputation and foot ulcers in diabetes
Health Intervention:	Foot screening with monofilament No screening
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Plantar ulcerations ▪ Amputations
Side Effects of the Intervention:	▪ Anxiety ▪ Inaccurate test result

Frequency of Foot Screening

Problem Formulation 26

Clinical Question:	Do programs that target patients at a high risk for foot disease decrease amputations or ulcers?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals on who, when, and how regarding foot monitoring for people with diabetes
Population:	Adults with type 1 and 2 diabetes
Health Problem:	Amputation and foot ulcers in diabetes
Health Intervention:	Population based program targeting high-risk people with diabetes No screening
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, health educators, registered dieticians, and RNs
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Plantar ulcerations ▪ Amputations
Side Effects of the Intervention:	▪ Anxiety ▪ Inaccurate test result

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 08/2007	0/129
	"Mass Screening"[MeSH] AND "diabetic foot /diagnosis"[MeSH]	Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 08/2007	1/3
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	2/2

Evidence Tables

Table 26.1: Identifying Patients with Diabetes at High-Risk for Lower-Extremity Amputations

Summary of a Cohort Study

Study Name	Design	Population	Groups	Results	Bias
Rith-Najarian SJ, et al. **Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting.** Diabetes Care 1992; 15: 1386-1389 [117] **Location:** US **Sponsor:** not stated	**Design:** Prospective Cohort **Follow-up:** 32-months	**Inclusion criteria**: Individuals on the Red Lake Indian Reservation diabetes registry **Exclusion criteria:** not stated **Baseline data:** The distribution of patients for risk categories 0, 1, 2, and 3 was 74.3, 8.4, 4.5, and 13% **Size:** 358 Native Americans	Patients were stratified into four risk categories based on sensation status to the 5.07 monofilament, the presence of foot deformity, and a history of lower-extremity events (amputation or ulceration): 0-sensate 1-insensate 2-insensate with deformity 3-history of lower extremity events Patients had a foot exam at least annually	41 patients developed ulcerations, and incidence rates correlated positively with increasing risk category p<0.00001 **Plantar Ulceration Rate:** Risk Category 0 6 (OR 1.0) Risk Category 1 8 9 (OR 15) Risk Category 2 170 (OR 32) Risk Category 3 330 (OR 78) Combining categories 1-3 = 90% sensitivity/86% specificity for predicting ulcerations **Amputations:** Risk Category 0 0 Risk Category 1 0 Risk Category 2 & 3 14	Sensitivity testing with monofilaments is semiquantitative Could not confirm whether changes in status at subsequent exam represented true changes in underlying neuropathy or were variations in the method

Table 26.2: Foot Screening and Follow-up Program

Summary of Meta-Analysis from Health Technology Assessment

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% Confidence Interval)	Adverse Effects	Author's Conclusions
Screening and Foot Protection Program Health Technology Assessment 2000; 4: 111-228 (118) References of studies included in the systematic review: McCabe CJ, et al. Evaluation of a diabetic foot screening and protection programme. Diabet Med. 1998;15(1):80-4 (120)	Last update: June 2000 Databases: ISI Science Citation Index, BIOSIS, BDAD, CINAHL, CISCOM, Cochrane Systematic Reviews, Cochrane Wounds Group, , CRIB, DARE, Dissertation Abstracts, DHSS Data, EconLit, EMBASE, Index to Scientific and Technicol Proceedings, MEDLINE, National Research Register, NHS Economic Evaluation Database, Royal College of Nursing Database, SIGLE Search Terms: Wound infection OR pilonidal cyst OR wounds and injuries OR wound healing OR leg ulcer OR varicose ulcer OR skin ulcer OR decubitis	Number of studies included: 1 RCT Intervention: Primary foot screening examination using Semmes-Weinstein monofilaments plus biothesiometry and palpation of foot pulses Any abnormality was reviewed at a second appointment where ankle/brachial pressure index, transcutaneous oxygen concentration and foot pressures were measured and x-rays were taken. Patients with foot deformities or history of ulceration or ABPI ≤0.75 were deemed high risk and entered into prevention (patients not meeting this criteria were designated low risk and received no further treatment) Prevention program included weekly appointments with podiatry at a diabetic foot clinic, hygiene maintenance, support hosiery, protective shoes, and education about foot hygiene and inspection Control group continued usual care Settings: UK Heterogeneity: N/A Sample size: 2001 diabetic patients recruited from weekly diabetes outpatient clinic All but 4 patients already had ulcers Duration of Trials: 2 years	Inclusion criteria: Deformities, history of ulcer or ABPI≤0.75 Age Range: Not stated	Incidence of ulceration: Control: 3.5% Intervention: 2.4% p>0.14 Incidence of ulcers progressing to amputation: Control: 66% Intervention: 29% p=0.006 NNT=2 Incidence of amputation (major/minor): Control: 25 (12/13) Intervention: 7 (1/6) p<0.04 total p<0.01 for major amputations p>0.15 for minor amputations	Not stated	The research in the area of the prevention and treatment of diabetic foot ulcers is extremely poor quality and relatively uninformative.

Table 26.2: Prevention of Amputation in Diabetes

Summary of Meta-Analysis from Health Technology Assessment

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Hunt D and Gerstein H. **Foot Ulcers in Diabetes** Clinical Evidence 2001;397-402 (119) **References of studies included in the systematic review:** Mason J, et al. A systematic review of foot ulcer in patients with type 2 diabetes mellitus. I: prevention. Diabet Med 1999;16:801-812 (121)	**Last update:** February 2001 **Databases:** Cochrane Trials Register, Medline, Embase, Cinahl, Social Science Citation, Index to Scientific and Technical Conference Proceedings (ISI), HMIC database, and SIGLE **Search Terms:** Not stated	**Number of studies included:** 1 systematic review (included 10 studies) **Intervention:** Usual care vs. diabetes screening and protection program Diabetes screening looked for deficits in pedal pulses, light touch (including monofilament) and vibration sensation People with persistent abnormal findings were referred to foot clinic if they had a history of foot ulcer, were found to have a low ankle-brachial index (<0.75), or had foot deformities Foot clinic provided podiatry, protective shoes, and education regarding foot care **Settings:** Not stated **Heterogeneity:** Not stated **Sample size range:** Not stated **Primary outcome of interest:** Not stated **Duration of Trials:** Follow-up lasted 2 years after enrollment	**Inclusion criteria:** Not stated **Age Range:** Not stated	**Amputation:** Control: 12 (1.2%) Interview: 1 (0.1%) ARR 1/1% (CI 0.4%, 1.9%) NNT=91 (CI 53, 250)	Not stated	Screening is beneficial

Self-Management

Self-Management Education

Problem Formulation 27

Clinical Question:	Does Diabetes Self-Management Education (DSME) lead to improved outcomes?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in promoting effective self-management skills
Population:	Adults with type 1 and 2 diabetes
Health Problem:	Type 1 and type 2 diabetes
Health Intervention:	▪ Diabetes Self-Management Education ▪ No treatment
Practitioners:	KP physicians, physician assistants, nurse practitioners, nurses, pharmacists, health educators, registered dieticians
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Improved functional/health status ▪ Improved quality of life ▪ Improved glucose control ▪ Improved weight ▪ Improved lipid profiles ▪ Decreased CV events ▪ Decreased mortality ▪ Decreased hospitalization

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus" [MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/20/2007	0/96
	"Diabetes Mellitus" [MESH] AND ("Self-Care"[MESH] OR "Patient Participation" [MESH] OR "Patient Education"[MESH])	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/20/2007	0/18
		Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 7/20/2007	0/185
	"Diabetes Mellitus" [MESH] AND ("Self-Care"[MESH] OR "Attitude to Health" [MESH])	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/20/2007	0/7
		Randomized, controlled trial, All Adult: 19+ years English, Human	1965 – 7/20/2007	0/164
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/

Evidence Table

Table 27.1: Diabetes Self-Management Education

Study, Total n	Study Population & Treatment Groups Size & Drug	Results	Comments
Norris, SL 2002 (Meta-Analysis) # studies found: # 72 # studies included: # 31	Characteristics of studies found RCTs Type 2 diabetes "health education" combined with "diabetes mellitus": Medline, ERIC, Cinahl Intervention: Diabetes Self-Management Education Total N: 4263	The goal of the meta-regression was to determine whether [DELTA]* was influenced by the time frame over which the intervention was delivered, the length of follow-up, the initial GHb, the number of contacts with subjects, or total contact time. During or immediately after the intervention: Significance level <0.05; Change in GHb (%) - 0.76; 95%CI -1.18 to –0.34 1-3 months: Significance level >0.10; Change in GHb (%) - 0.26; 95%CI -0.73 to 0.21 ≥ 4 months: Significance level >0.10; Change in GHb (%) - 0.26; 95%CI -0.48 to –0.05 GHb decreased more with additional contact time between participant and educator; a significant decrease of 1% was noted for every additional 23.6 hours of contact. The benefit declines 1-3 months after the intervention ceases, however, suggesting that learned behaviors change over time. *[DELTA] = the mean difference between the intervention and the control group.	Conclusions DSME is effective for individuals with type 2 diabetes on glycemic control Duration of contact time between educator and patient was the only significant predictor of effect, with 23.6 h of contact time needed for each 1% absolute decrease in GHb. Biases, etc. English language bias Publication bias Only RCTs

Self-Monitoring of Blood Glucose in Type 1 and Type 2 Diabetes

Problem Formulation 28 & 29*

Clinical Question:	Should patients with diabetes self-monitor their blood glucose?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 and 2 diabetes.
Population:	All adults with type 1 and 2 diabetes
Health Problem:	Hyperglycemia
Health Intervention:	▪ Self-Monitoring of Blood Glucose ▪ Self-Monitoring of Urine ▪ No treatment Interventions were compared with each other, not in combination.
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, RNs, registered dieticians, and health educators
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Improved quality of life ▪ Decreased intermediate outcomes: HbA1c/GHb
Side Effects of the Intervention:	▪ Decreased Quality of Life ▪ Increased intermediate outcomes: hyperglycemia, hypoglycemia

* This problem formulation was originally two separate problem formulations, one for type 1 and the other for type 2. In the 2010 iteration of this guideline they were combined into one problem formulation.

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials. Because searches on this topic were conducted previously, updates to those searches were performed.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH]	Meta-analysis, All Adult: 19+ years, English, Human	1965 – 7/20/2007	0/132
PubMed	(((((("diabetes mellitus" [MeSH Terms] OR Diabetes mellitus[Text Word]) AND ((("self- care"[MeSH Terms] OR self-care[Text Word]) OR ("blood glucose self-monitoring"[MeSH Terms] OR blood glucose self-monitoring[Text Word])) OR ("patient compliance"[MeSH Terms] OR patient compliance[Text Word]))) AND ((((("glucose"[MeSH Terms] OR glucose[Text Word]) AND (("blood"[Subheading] OR "blood"[MeSH Terms]) OR blood[Text Word])) AND levels[All Fields]) OR ("urinalysis"[MeSH Terms] OR urinalysis[Text Word]))))	Randomized, controlled trial, All Adult: 19+ years English, Human	1/2001 – 7/20/2007	0/79
Health Technology Assessments	Diabetes	Systematic reviews	N/A	4/16
Cochrane	No terms used - searched list of systematic reviews by Cochrane Metabolic and Endocrine Disorders Group	Systematic reviews	7/15/05	0/47
Clinical Evidence (Volume 13, June 2005)	No terms used - searched book by Endocrine Disorders	Systematic reviews and RCTs	7/15/05	0/0

Self-Titration of Insulin

Problem Formulation 30

Clinical Question:	Does self-titration of insulin lead to an improvement in diabetes outcomes, including A1c control?
Intended Use of the Guideline:	To assist primary care physicians and other health care professionals in counseling and treating all adults with type 1 or 2 diabetes.
Population:	All adults with type 1 or 2 diabetes
Health Problem:	Hyperglycemia
Health Intervention:	▪ Self-managed, algorithm-driven titration of insulin dosage ▪ Physician-managed, algorithm-driven titration of insulin dosage
Practitioners:	KP physicians, physician assistants, nurse practitioners, pharmacists, RNs, registered dieticians, and health educators
Setting:	Outpatient office visit
Most Important Health Outcomes Associated with the Intervention:	▪ Quality of life ▪ Intermediate outcomes: HbA1c/GHb
Side Effects of the Intervention:	▪ Quality of life ▪ Increased intermediate outcomes: hyperglycemia, hypoglycemia

Search Strategy

Studies reviewed included only systematic reviews and randomized, controlled trials.

Database:	Terms:	Article type and Limits:	Time Frame:	No. Included / Total Retrieved
PubMed	"Diabetes Mellitus"[MeSH Terms] AND "Self-Care"[MeSH Terms]	Meta-analysis, All Adult: 19+ years, English, Human	1966 – 7/28/2007	0/6
	"Diabetes Mellitus"[MeSH] AND "Self-Care"[MeSH Terms]	Randomized, controlled trial, All Adult: 19+ years English, Human	1966 – 7/28/2007	7/215

Evidence Table

Table 30.1: Effect of Self-Titration of Medication on HbA1c (randomized open-label trials)

Name	N	Mean ages (years/SD)	% female	Follow-up Rate	Follow-up Time	Mean ± SD Baseline HbA1c (%)	Follow-up HbA1c %	Effect Difference	p	Study Quality†	Biases*
Gerstein, 2006	Insulin 206 OAs 199	56.3±9.4 56.8±10.1	33.0 35.2	95.6% 97%	24 weeks	8.6±1.0 8.5±1.0	-1.55 -1.25	0.30%	0.005	2	N
Comments: No differences in hypoglycemia were noted. Significant support provided by pharmaceutical manufacturer.											
Kennedy, 2006	UT/lab 1491 UT/POC 1363 AT/lab 1501 AT/POC 1366	57±11 57±12 57±12 57±11	48 47 51 50	81.0%	24 weeks	8.9±1.5 8.9±1.6 8.9±1.6 8.9±1.5	UT –1.3 AT –1.5	0.2%	<0.0001	2	N
Comments: No differences in hypoglycemia were noted. Sponsored by pharmaceutical manufacturer											
Yki-Jarvinen, 2006	Glargine 61 NPH 49	56±1 57±1	38 35	98.2%	36 weeks	9.13±0.15 9.26±0.15	7.14±0.12 7.16±0.14	NS	N/A	2	N
Comments: Lower incidence of hypoglycemia in glargine group in 1st 12 weeks of treatment, no difference thereafter. Significant support from pharmaceutical manufacturers											
Davies, 2005	MD-led 2315 Pt-led 2273	57.6±10 57.5/10.1	52.7 50.3	91% 91%	24 weeks	8.9±1.3 8.9±1.3	7.9±1.2 7.7±1.2	0.2%	<0.001	2	N
Comments: Very large study group recruited from primary care and specialty practice settings. No differences in hypoglycemia were noted.											
Janka, 2005	Glargine/OA 177 Insulin 70/30 187	60.9±8.7 60.4±9.1	39 43	96% 85%	24 weeks	8.85±0.98 8.83±0.87	7.15±0.90 7.49±1.09	-1.34% (95% CI -0.53 to 0.16%)	0.0003	3	N
Comments: Large dropout rate in 70/30 group. Incidence of minor hypoglycemic episodes greater in 70/30 group. Supported by pharmaceutical manufacturer.											
Raskin, 2005	Insulin 70/30 117 Glargine 116	52.6±10.6 52.3±9.8	47 44	85% 94%	1 year	9.7±1.5 9.8±1.4	6.91±1.17 7.41±1.24	0.50%	0.01	3	N
Comments: Supported by pharmaceutical manufacturer. Large dropout rate in 70/30 group. Incidence of hypoglycemia greater in 70/30 group.											
Riddle, 2003	Glargine 367 NPH 389	55±9.5 56±8.9	55 56	91% 91.8%	24 weeks	8.61±0.9 8.56±0.9	6.96 6.97	0.03% (95% CI -0.13 to 0.08%)	NS	3	N
Comments: Hypoglycemic events were more frequent in the NPH-treated group. Sponsored by pharmaceutical manufacturer.											

AT = active titration; lab = laboratory HbA1c determination; NS= not reported; N/A = not available; OA = oral agents; POC = point-of-care HbA1c determination; Pt = patient; UT = usual titration

† Study quality measured by Jadad trials scoring system

* Biases: N: None; 1: Sample attrition >15%; 2: Sample selection bias; 3: Detection bias (e.g., measurement error, power); 4: Study Procedure biases

Table 30.2: Self-Monitoring of Blood Glucose in Type 2 Diabetes

Summary of Meta-Analysis from Health Technology Assessment

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Coster S, et al. Monitoring blood glucose control in diabetes mellitus: a systematic review. Effectiveness of self-monitoring in type 2 diabetes mellitus. Health Technol Assess. 2000;4:i-93 (124) References of studies included in the systematic review: Allen BT, et al. Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus. Randomized, controlled trial comparing blood and urine testing. Diabetes Care 1990;13:1044-50 (129) Estey A, et al. Follow-up intervention: its effect on compliance behavior to a diabetic regimen. Diabetes Educator 1990;16:291-5 (144) Fontbonne A, et al. Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? Results of a randomized comparative trial. Diabetes Metab 1989;15:255-60 (145) Gallichan MJ. Self-monitoring by patients receiving oral hypoglycemic agents: a survey and a comparative trial. Practical Diabetes 1994;11:28-30 (146) Miles P, et al. Comparison of blood or urine testing by patients with newly diagnosed non-insulin dependent diabetes: patient survey after randomized crossover trial. Br Med J 1997;315:348-9 (147) Muchmore DB, et al. Self-monitoring of blood glucose in overweight type 2 diabetic patients. Acta Diabetol 1994;31:215-19 (148) Rutten G, et al. Feasibility and effects of a diabetes type II protocol with blood glucose self-monitoring in general practice. Family Pract 1990;7:273-8 (149) Wing RR, et al. Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type II diabetes? Am J Med 1986; 81:830-6 (150)	Last update: June 2000 Databases: Medline Embase Science Citation Index and Social Science Citation Index Search Terms: Diabetes mellitus (insulin-dependent diabetes mellitus or juvenile diabetes mellitus or maturity onset diabetes mellitus or non-insulin-dependent diabetes mellitus or pregnancy diabetes mellitus) AND (self-care OR blood glucose self-monitoring OR patient compliance) AND (glucose blood levels OR urinalysis).	Number of studies included: 8 RCTs (10 excluded) Intervention: Blood testing, urine testing and no testing in patients with type 2 diabetes No study required patients to modify their drug therapy in accordance with their self-monitoring results Most required tests before meals or 2 hours after meals, otherwise frequency varied from 6x/daily to 2x/ every other day Settings: France, The Netherlands, UK, Canada, US Heterogeneity:Not stated Sample size range:27-108 Primary outcome of interest: 3 studies HbA1c, 1 study HbA1, 3 studies GHb 1 study fructosamine Duration of Trials: 2 studies 52 weeks, 1 study 44 weeks, 4 studies 24 weeks 1 study 16 weeks	Inclusion criteria: 2 studies included patients on oral hypoglycemic drugs or insulin 6 studies only included patients not on insulin 2 studies focused on patients who were obese 2 studies recruited patients with poor control 1 study looked at newly diagnosed patients Age Range: Either >35 and <65 or >40 and <65 (Patients could be of any age)	Blood/Urine monitoring vs. no monitoring: One study found a small but significant decrease in HbA1c, but no patients lost weight (effect confounded with a range of differences in patient management between groups) 4 studies found a positive effect of monitoring on GHb pooled effect –0.25% (-0.61, 0.10) and body weight –0.28kg (-1.48, 0.93) Blood vs. urine monitoring: 3 studies found neither blood nor urine testing effect blood glucose control 1 study suggested urine and blood monitoring were equally effective Patient outcomes: 4 studies found no impact on quality of life	70% preferred urine testing to blood testing in 1 study and 71% in another	Self-monitoring of blood or urine was not effective at improving blood glucose control nor effecting body weight in type 2 diabetes There is anecdotal evidence of monitoring detecting hypoglycemia There is no evidence that blood glucose monitoring is more effective that monitoring urine Studies reviewed had low statistical power and were poorly conducted and reported and further research is needed

Note: Comparisons that are not stated in the results column were not disclosed by the author.

Table 30.3: Self-Monitoring of Blood Glucose in Type 1 Diabetes

Summary of Meta-Analysis from Health Technology Assessment

Author & Title	Last updated & Search Database	Study Characteristics	Characteristics of Study Participants	Results (95% CI)	Adverse Effects	Conclusions
Coster S, et al. Monitoring blood glucose control in diabetes mellitus: a systematic review. Effectiveness of self-monitoring in type 1 diabetes mellitus. Health Technol Assess. 2000;4:i-93 (124) References of studies included in the systematic review: Daneman D, et al. The role of self-monitoring of blood glucose in the routine management of children with insulin-dependent diabetes mellitus. Diabetes Care. 1985;8(1):1-4 (125) Gordon D, et al. Do different frequencies of self-monitoring of blood glucose influence control in type 1 diabetic patients Diabet Med. 1991;8(7):679-82 (151) Mann NP, et al. A prospective study to evaluate the benefits of long-term self-monitoring of blood glucose in diabetic children. Diabetes Care 1984;7(4):322-6 (152) Miller FW, et al. Blood testing compared with urine testing in the long-term control of diabetes. Arch Dis Child 1983;58:294-7 (153) Starostina EG, et al. Effectiveness and cost-benefit analysis of intensive treatment and teaching programmes for type 1 (insulin-dependent) diabetes mellitus in Moscow--blood glucose vs. urine glucose self-monitoring. Diabetologia 1994;37(2):170-6 (154) Terent A, et al. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a representative population. Acta Med Scand. 1985;217(1):47-53 (155) Worth R, et al. Intensive attention improves glycaemic control in insulin-dependent diabetes without further advantage from home blood glucose monitoring: results of a controlled trial. Br Med J (Clin Res Ed) 1982;285(6350):1233-40 (156) Careny, et al. The effects of blood glucose testing vs. urine sugar testing on the metabolic control of insulin-dependent diabetic children. Diabetes Care 1983;6:378-80 (126)	Last update: June 2000 Databases: Medline Embase Science Citation Index and Social Science Citation Index Search Terms: Diabetes mellitus (insulin-dependent diabetes mellitus or juvenile diabetes mellitus or maturity onset diabetes mellitus or non-insulin-dependent diabetes mellitus or pregnancy diabetes mellitus) AND (self-care OR blood glucose self-monitoring OR patient compliance) AND (glucose blood levels OR urinalysis).	Number of studies included: 24 studies found (8 controlled, 16 non-controlled) Intervention: 6 studies compared urine testing with blood testing 1 study compared blood testing with no testing (educational program) 1 study evaluated different blood testing frequencies 7 studies encouraged patients to change therapy in response to monitoring results Frequency of testing differed by study: 2 studies tested 3x/day, 2 studies tested 2x/day 1 study tested 2x/week (before meals and before bed) 1 study tested 2x/week (before and after meals and before bed), 1 study tested 2x/week, 1x/week, or daily, 1 study tested 2 days within 2 weeks Settings: Russia, Sweden, UK, US Heterogeneity: The fixed- and random-effects models find the same results and suggests that monitoring has either a constant or no effect Sample size range: 16-68 Primary outcome of interest: 3 studies HbA1c, 2 study HbA1, 3 studies GHb Duration of Trials: 24 weeks, 3 months, 5 months, 6 months, 18 months, and 2 years	Inclusion criteria: Patients on twice daily insulin injections (1 study included patients on a mixture of injections once and twice daily) Some patients recruited from inpatient treatment for diabetes-related complications; some patients already self-monitoring and had diabetes for >12 months; some required to not be pregnant nor have renal disease or retinopathy; some required to have had diabetes <20 years Age Range: 4 studies included children <18	Blood vs. urine monitoring: Estimated effect of blood monitoring on GHb was about –0.567% (-1.073, -0.061) in favor of blood monitoring	Most studies showed that patients preferred blood monitoring to urine testing Occurrences of hypoglycemia were low	Several trials concluded that self-monitoring has an effect by getting patients to focus on intensive management of their diabetes, but the staff and patients caused the metabolic improvements rather than the monitoring itself

Appendix C: ADA Evidence Grading System

Table 1—*ADA evidence grading system for clinical practice recommendations*

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison to historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

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