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

Russell Harris, MD, MPH; Katrina Donahue, MD, MPH; Saif S. Rathore, MPH; Paul Frame, MD; Steven H. Woolf, MD, MPH; Kathleen N. Lohr, PhD

Epidemiology

The prevalence of type 2 diabetes mellitus (diabetes) in the United States is growing[1,2]; the burden of suffering caused by its complications is heavy[3] and may also be growing. These complications include increased risk of cardiovascular disease (CVD),[4] end-stage renal disease (ESRD),[5,6] blindness,[7] and amputation of the lower extremities.[8,9] The magnitude of the risk for these complications varies among persons with a new clinical diagnosis of diabetes. After 10 years, more than 20% of such persons will have suffered a major cardiovascular event (eg, myocardial infarction, stroke, heart failure, or sudden death), fewer than 5% will have developed blindness, and fewer than 2% will have developed ESRD or had lower extremity amputation.[10]

Three general approaches to reducing the complications of diabetes are (1) preventing the occurrence of diabetes in the first place, (2) improving care for persons who have already received a diagnosis, and (3) screening asymptomatic persons for diabetes.[11] By *asymptomatic*, we mean persons without both the direct symptoms of hyperglycemia (eg, polyuria) and the symptoms of associated conditions (eg, infections or angina pectoris). We distinguish between detection of diabetes due to the presence of these symptoms and detection of diabetes by screening, either systematic screening or the haphazard screening that occurs with frequent use of multichannel chemistry profiles. Our review focuses on the evidence for the effectiveness of systematic screening for diabetes as opposed to no screening.

Interest in screening has been prompted by research showing that approximately one-third of persons who meet criteria for diabetes have not received a diabetes diagnosis.[12] In 1996, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against screening for diabetes.[13] Since that USPSTF review, new evidence concerning the effectiveness of various treatments to prevent complications has fueled

From: Cecil G. Sheps Center for Health Services Research, Department of Medicine, University of North Carolina at Chapel Hill (Harris), Chapel Hill, NC; Department of Family Medicine, University of North Carolina at Chapel Hill (Donahue), Chapel Hill, NC; Department of Internal Medicine, Section of Cardiovascular Diseases, Yale University School of Medicine (Rathore), New Haven, CT; Tri-County Family Medicine (Frame), Cohocton, NY; Department of Family Practice, Virginia Commonwealth University (Woolf), Fairfax, VA; RTI International, Research Triangle Park, NC and School of Public Health, University of North Carolina at Chapel Hill (Lohr), Chapel Hill, NC.

Address correspondence to: Russell Harris, MD, MPH, Sheps Center for Health Services Research, 725 Airport Road, CB# 7590, Chapel Hill, NC 27599-2949, Phone: 919-966-2949, Fax: 919-966-3911, E-mail: rharris@med.unc.edu.

Request for reprints: Reprints are available from the AHRQ Web site at www.preventiveservices.ahrq.gov and in print through the AHRQ Publications Clearinghouse (call 1-800-358-9295 or E-mail ahrqpubs@ahrq.gov).

The USPSTF recommendations based on this review can be found in "Screening for Type 2 Diabetes Mellitus in Adults: Recommendations and Rationale," available on the AHRQ Web site and through the AHRQ Publications Clearinghouse.

This chapter first appeared as an article in *Ann Int Med*. 2003;138: 215-229.

continued controversy about the effectiveness of screening.[14-22] To assist the USPSTF in updating its recommendation, we performed a systematic review of the evidence concerning screening adults for diabetes.

Methods

To guide our literature search, we used USPSTF methods to develop an analytic framework with linkages that represent 5 key questions in a logical chain between screening and health outcomes.[23] We developed eligibility criteria for admissible evidence for each key question, focusing on screening strategies that are feasible in a primary care environment and on high-quality evidence about health outcomes (as contrasted with intermediate outcomes) of treatment for newly diagnosed diabetes.

We examined the critical literature from the 1996 USPSTF review and searched MEDLINE and the Cochrane Library for reviews and relevant studies published in English between January 1, 1994, and July 30, 2002. We also examined key articles published before 1994 and articles found by examining the reference lists of pertinent reviews or suggested by experts.

The first author and at least 1 co-author or trained assistant reviewed abstracts and articles to find those that met eligibility criteria (see Appendix Table 1). For included studies, 2 reviewers abstracted relevant information using standardized abstraction forms and graded the quality of the study according to USPSTF criteria.[23] Important articles on which a recommendation could rest were examined and discussed by all authors. We distributed a draft systematic evidence review for external peer review, soliciting comments from experts, relevant professional organizations, and federal agencies, and made revisions based on feedback.

A more complete account of the methods used in this review can be found in the Appendix. The complete systematic evidence review is available on the Agency for Healthcare Research and Quality Web site (www.ahrq.gov).[24] This evidence report was funded through a contract to the Research Triangle Institute-University of North Carolina Evidence-based Practice Center from the Agency for Healthcare Research and Quality (AHRQ). Staff of the funding agency and members of the USPSTF contributed to the study design, reviewed draft and final manuscripts, and made editing suggestions.

Results

For the USPSTF to conclude that screening reduces diabetic complications, the evidence must demonstrate that feasible screening tests can detect diabetes during a preclinical phase and that the knowledge of the diagnosis of diabetes in this phase will lead to earlier treatment that will reduce complications more than would treatment begun after clinical detection. Further, the magnitude of this "additional benefit" (ie, the reduction in complications from initiation of treatment in the preclinical phase minus the reduction in complications from starting treatment after clinical diagnosis) must be great enough to outweigh the harms and effort of screening.

Does Diabetes Have an Asymptomatic Preclinical Phase and How Long Is It?

The natural history of diabetes includes an asymptomatic preclinical phase. Many people who meet criteria for diabetes have not received a diabetes diagnosis. In the third National Health and Nutrition Examination Study (NHANES III), conducted between 1988 and 1994, the prevalence of diagnosed diabetes among people 20 years of age and older was 5.1%; the prevalence of previously undiagnosed diabetes was 2.7%.[12] Rates of diagnosed diabetes for non-Hispanic black and Mexican-American persons were 1.6 and 1.9 times the rate for non-Hispanic white persons, and the rates of undiagnosed diabetes were similarly higher.

The length of this asymptomatic period is less clear. No study has compared a screened with a comparable unscreened sample to determine the difference in the time at which diabetes is diagnosed. One group used an indirect approach to calculate this interval. After making assumptions about the rate of development of diabetic

retinopathy early in diabetes, Harris et al[25,26] estimated that the preclinical period lasted between 10 and 12 years. According to this calculation, screening a previously unscreened population would detect diabetes, on average, 5 to 6 years before clinical diagnosis. Even if this estimate is accurate, however, it represents a mean value. Some people will have a longer, and some a shorter, asymptomatic period. The true mean length of this period and the distribution of its length are unknown.

How Accurate Are the Screening Tests?

Determining the accuracy of screening tests for diabetes is complicated by uncertainty about the most appropriate reference standard. Two standards of diagnosis are in general use: one based on the 2-hour post-load plasma glucose (2-hPG) test and the other based on the fasting plasma glucose (FPG) test.[27-29] The standard cutpoint for the 2-hPG test is 11.1 millimoles per liter (mmol/L) [200 milligrams per deciliter (mg/dL)]; the FPG cutpoint is 7.0 mmol/L (126 mg/dL). Both tests require a second confirmation. Hemoglobin A1c (HbA1c), using various cutpoints, is a third test that has been proposed as a standard reference for diagnosing diabetes.[30-32]

It is not clear which of these tests and cutpoints most closely predicts diabetic complications.[33] The cut-point for the 2-hPG test was based on a threshold that predicted retinopathy prevalence in several studies.[27,28] The FPG cutpoint was chosen to correspond to that for the 2-hPG test.[27,28] All three tests (2-hPG, FPG, HbA1c) are associated with future cardiovascular events in a linear fashion both above and below the present diabetes cutpoints, with no obvious threshold.[34-39] However, experts have set the point at which hyperglycemia is termed diabetes without considering CVD prediction.

When a 2-hPG of $\geq$ 11.1 mmol/L (200 mg/dL) is used as the reference standard, the specificity of an FPG level with a cut-point of 7.0 mmol/L (126 mg/dL) is greater than 95%; the sensitivity is about 50% and may be lower for persons older than age 65 years of age.[40] Among a general previously nondiabetic sample of persons 40 to 74 years of age, a person with an FPG level of 7.8 mmol/L (140 mg/dL) or greater has a 91% probability of having a 2-hPG level of $\geq$ 11.1 mmol/L (200 mg/dL). For an FPG between 7.0 mmol/L (126 mg/dL) and 7.8 mmol/L (140 mg/dL), the probability is 47%.[41] HbA1c level is more closely related to FPG than to 2-hPG level,[42] but it is not sensitive to low levels of hyperglycemia.[30] Reliability is higher for FPG than for HbA1c or 2-hPG level.[43-45] Although the reliability of the HbA1c assay has been a concern, it is not as grave a problem.[43]

In clinical practice, requiring a screening test to be fasting (as with the FPG) or post-load (as with the 2-hPG test) presents logistical problems. In a recent study in primary care settings, random capillary blood glucose with a cutpoint of 6.7 mmol/L (120 mg/dL) had a sensitivity of 75% and a specificity of 88% for detecting people who have positive results on FPG assay or on 2-hPG assay.[46]

Does Earlier Knowledge of Diabetes After Screening Lead to Better Treatment and Improved Health Outcomes?

We examine here the extent to which earlier application of available treatments for diabetes would improve health outcomes.

Tight Glycemic Control

Five randomized controlled trials (RCTs) have compared health outcomes in groups that differ with respect to glycemic control (Table 1).[10,47-57] Four of these studies,[48-56] although generally well conducted, were small and lacked power to detect clinically important differences between groups. The longest and largest study was the United Kingdom Prospective Diabetes Study (UKPDS), an RCT of 3,867 people with newly diagnosed diabetes over 10 years.[10] Because the UKPDS intervention was not blinded, outcomes that involve clinician judgment (such as whether to use retinal photocoagulation) could have been biased.[58]

The primary UKPDS analysis found a nonsignificant trend (relative risk [RR] = 0.84;

Table 1: Randomized controlled trials of tight glycemic control

Study (quality)	Study years	Groups (patients)	Glycemic control	Renal failure
UGDP, 1971[48] 1978[49] (fair)	8.75	Placebo: n = 204 Insulin variable: n = 198	22.8% increase* 13.5% decrease*	NR
UKPDS 33 1998[10] (good)	10	Conventional therapy: n = 1,138 Intensive therapy: n = 2,729	7.9%† 7.0%†	< 1% < 1% (*P* = 0.45)
UKPDS 34 1998[47] (good)	10.7	Conventional therapy: n = 411 (primarily diet) Intensive therapy: n = 342 (metformin)	8.0%† 7.4%†	<1% <1% (*P* = 0.90)
Kumamoto, 1995[55] 2000[51] (fair)	8	Conventional therapy: n = 50 Intensive therapy: n = 52	9.4%† 7.1%†	NR
VA CSDM 1997[52] 1996[54] 1995[56] 1999[50] 2000[57] (fair)	2.25	Standard therapy: n = 78 Intensive therapy n = 75	9.2%† 7.1%†	NR
Steno 2, 1999[53] (fair)	3.8	Standard therapy: n = 80 Intensive therapy: n = 80	9.0%† 7.6%†	0 0

* change in fasting blood glucose from baseline

† Median hemoglobin A1C

NR indicates not reported; Steno, Steno type 2 randomized study; UGDP, University Group Diabetes Program; UKPDS, UK Prospective Diabetes Study Group; VA CSDM, VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes.

Table 1: Randomized controlled trials of tight glycemic control (continued)

Severe visual impairment	Myocardial infarction	Stroke	Amputation	All-cause mortality
Acuity = 20/200 either eye	Significant ECG abnormality			
11.2%	20%	NR	1.5%	26.3%
11.4%	17.6%		1.6%	24.0%
(NS)	(NS)		(NS)	(NS)
Vision too poor to drive				
11%	16.3%	4.8%	1.6%	18.7%
11%	14.2%	5.4%	1.0%	17.9%
(NS)	(*P* = 0.052)	(*P* = 0.052)	(*P* = 0.099)	(*P* = 0.044)
Blind in one eye				
3.2%	17.8%	5.6%	2.2%	21.7%
3.5%	11.4%	3.5%	1.8%	14.6%
(*P* = 0.87)	(*P* = 0.001)	(*P* = 0.13)	(*P* = 0.57)	(*P* = 0.011)
NR	Major CVD event 1.3 events/100 P-y 0.6 events/100 P-y NS			NR
Unilateral or bilateral visual impairment				
9.0%	5.1%	2.6%	0	5.1%
6.7%	6.7%	6.7%	1.3%	6.7%
(NS)	(NS)	(NS)	(NS)	(NS)
Blind in one eye	Nonfatal	Nonfatal		
9.0%	5.1%	10.2%	5.1%	2.6%
1.3%				
(*P* = 0.03)	5.2%	1.3%	5.2%	5.2%
	(NS)	(NS)	(NS)	(NS)

95% confidence interval [CI] 0.71-1.0) toward a reduction in myocardial infarction (MI) for tight versus less tight glycemic control groups but no difference in any other cardiovascular outcome.[10] The absolute difference in MI events was 2.1% over 10 years, entirely in nonfatal events. Three other studies found no statistically significant difference in cardiovascular outcomes from tight glycemic control.[48,49,51,52,56] The most positive study, a UKPDS analysis, had puzzling results.[47] It found that metformin reduced MI and all-cause mortality compared with conventional glycemic control (Table 1). Further analyses, however, showed that these benefits were out of proportion to the achieved glycemic control and disappeared when all patients taking metformin (including those who had metformin added to another treatment) were considered.[47]

In three of the studies, tight glycemic control reduced the progression of albuminuria and retinopathy.[10,51,57] Although this important finding in intermediate outcomes may herald future clinical benefits, few people in any group in these trials developed the clinical outcomes of ESRD or blindness (Table 1). One study of a multifactorial intervention that included more than tight glycemic control[53] found a statistically significant reduction in severe visual impairment in the intervention group; in the other studies, groups did not differ in the development of severe visual impairment or ESRD.

Only 2 of these trials included people with diabetes who had received recent diagnoses[10,49]; in neither study was diabetes detected primarily by screening. Thus, these studies provide information about the effect of tight glycemic control among people whose diabetes has been detected clinically. Compared with tight glycemic control after clinical detection, the added benefit of earlier tight glycemic control after detection by screening (at a time when glycemic levels are often only slightly elevated), is unknown but probably small over at least 15 years after diagnosis.

Antihypertensive Treatment

Earlier knowledge of diabetes status could affect treatment for hypertension during the preclinical period by changing the intensity of treatment or the choice of antihypertensive drug. The optimal target blood pressure is lower for hypertensive patients with diabetes than for those without. The Hypertension Optimal Treatment (HOT) trial found that diabetic persons randomly assigned to a target diastolic blood pressure of 80 mm Hg had a reduction in CVD and all-cause mortality compared with diabetic persons in the group with a target of 90 mm Hg, but there were no differences among nondiabetic persons randomly assigned to the same blood pressure target groups (Table 2).[59] Three other RCTs (one in normotensive diabetics) support the conclusion that more intensive blood pressure control reduces stroke, diabetes-related death, and all-cause mortality for in persons with diabetes (Table 2).[60-62]

These four RCTs were acceptable in quality. Although blinding caregivers and participants was difficult, endpoint assessment was blinded in all four trials. Four percent of participants or fewer were lost to follow up for mortality endpoints. The trials used various antihypertensives.

Ten RCTs and 3 meta-analyses have compared clinical outcomes among diabetics treated with various antihypertensives[62-76] (Tables 3 and 4). Two issues addressed by these studies are whether calcium antagonists (CAs) provide less benefit to diabetic persons than to nondiabetic persons (and thus should be avoided) and whether agents that interrupt the renin-angiotensin system (eg, angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blocking [ARB] agents) provide greater benefit to diabetic than to nondiabetic persons (and thus should be prescribed).

The evidence concerning the effects of CAs among diabetic persons is mixed. Hypertensive persons taking CAs compared with those taking other drugs may have a somewhat increased risk for MI and congestive heart failure and a decreased risk of stroke; drug groups do not differ in all-cause mortality (Tables 3 and 4). Although these trends may be

slightly more pronounced for diabetic persons, the effects of CAs are not qualitatively different between persons with and without diabetes.[73]

Some evidence suggests that, compared with most other antihypertensive drugs, ACE inhibitors or ARBs provide better protection against CVD events (more so for MI than for stroke) and renal disease, an effect that may be partly independent of blood pressure reduction. Five of six RCTs that have compared ACE inhibitors or ARBs with other agents in diabetic persons with hypertension have found a reduction in some CVD outcomes in the ACE inhibitor or ARB group, even after adjusting for differences in blood pressure (Table 3).[62-64,66-68,74-76] The Losartan Intervention for Endpoint reduction study, for example, found that, for diabetic patients with hypertension, the ARB losartan reduced all-cause mortality compared with the beta-blocker atenolol, a result that was less certain for hypertensive patients without diabetes.[75] ACE inhibitors or ARBs also reduce the development of diabetic nephropathy[77-82] and its progression to ESRD[71,83,84] more than most other antihypertensive agents.

One large study of hypertensive diabetic persons showed no benefit of an ACE inhibitor compared with a beta-blocker for either CVD or renal outcomes[63]; another study of normotensive diabetics found no difference in outcomes between treatment with an ACE inhibitor compared with a CA (Table 3).[62] The discrepancy between these results and other studies has not been satisfactorily explained. The benefits of ACE inhibitors and ARBs over other antihypertensive drugs are also unclear for nondiabetic persons,[68,72,74-76] especially those at lower CVD risk. A large meta-analysis of studies of predominantly nondiabetic persons found that ACE inhibitors provided no CVD benefit over other types of drugs (mostly diuretics and beta-blockers) in the treatment of hypertension (Table 4).[72] (See Addendum.)

We should be cautious in drawing conclusions from these studies for several reasons. First, many trial participants required more than a single drug to attain their target blood pressures, making head-to-head comparisons of particular drugs difficult. Second, the meta-analyses grouped specific drugs within a class together. Drugs within a class, however, may have different effects. Third, the patients studied in these trials differed in many respects, including age, presence of co-morbid conditions, degree of hypertension, duration of diabetes, and presence of other cardiovascular risk factors. Nonetheless, the meta-analyses compare results across trials. Drug effects that vary by patient group make it more difficult to identify the effects of a single drug or drug class. Finally, although these trials are generally acceptable in quality, they vary in such important issues as blinding procedures and withdrawal rates (Table 3).

Thus, the current evidence favors the conclusion that diabetic patients benefit from more intensive blood pressure control than nondiabetic patients. It remains uncertain whether diabetic patients should be treated with different antihypertensive medications than nondiabetic patients. Although the studies reviewed included diabetic persons whose disease presumably had been detected clinically, CVD risk is still increased twofold or more among people with undiagnosed diabetes.[34-39,85] Direct evidence shows that among diabetics with this degree of risk, an aggressive approach is beneficial within a 5-year time frame, the estimated mean time before clinical diagnosis.

Treatment of Dyslipidemia and the Use of Aspirin

Although people with diabetes do not have higher total cholesterol or low-density lipoprotein cholesterol (LDL-C) levels than similar nondiabetic persons, they have higher levels of triglycerides and lower levels of high-density lipoprotein cholesterol (HDL-C).[86] They may also have a tendency toward thrombosis.[87,88] Knowledge of diabetes during the preclinical period could influence treatment for coronary heart disease (CHD) risk by changing the use of aspirin or the intensity or type of treatment for dyslipidemia.

RCTs of both primary and secondary prevention have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and fibric

Table 2: Studies of intensity of treatment with antihypertensive medications

Study (quality)	Study Age *y*	N groups (patients)	Blood pressure control	Myocardial infarction
UKPDS-38 1998[60] (fair)	8.4	Less tight blood pressure control: 390	154/87	23.5*
Patients with diabetes and hypertension	56-57	Tight: 758	144/82	18.6 (*P* = 0.13)
HOT, 1998[59]	3.8	Target DBP		
Diabetes subgroup (fair)	61.5	≤90‡: 501	143.7/85.2	7.5*
		≤85: 501	141.4/83.2	4.3
		≥80: 499	139.7/81.1	3.7 (*P* = 0.11)
ABCD, 2000[61]	5	Moderate blood pressure control: 233	138/86	No difference
Patients with hypertension and diabetes (fair)	57	Intensive: 237	132/78	
ABCD 2002[62]	5.35	Moderate blood pressure control: 243	137/81	6.2%
Normotensive patients with diabetes (fair)	58-59	Intensive: 237	128/75	8.0% (*P* = 0.43)

* per 1000 patient-years

† p - y = person-years

‡ target diastolic blood pressure (mmHg)

§ percentage with marked deterioration in vision

ABCD indicates Appropriate Blood Pressure Control in Diabetes; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HOT, Hypertension Optimal Treatment; MI, myocardial infarction; NR, not reported; UKPDS-38, UK Prospective Diabetes Study Group.

Table 2: Studies of intensity of treatment with antihypertensive medications (continued)

Stroke	Death from CVD events	Non-CVD outcomes		Adherence withdrawal	Blinding comments
11.6*	DM mortality 20.3*	ESRD 2.3*	Vision 19.4%	No drug 43% p-y†	Open label; blinded
6.5 (*P* = 0.013)	13.7 (*P* = 0.019)	1.4 (*P* = 0.29)	10.2% (*P* = 0.004)	No drug 6% p-y† 4% study withdrawal	outcome assessment
9.1* 7.0 6.4 (*P* = 0.34)	CVD mortality* 11.1* 11.2 3.7 (*P* = 0.016)	NR		%DBP > 90 mmHg 12% 7% 6% 2.6% study withdrawal	Open label; blinded outcome assessment
No difference	All-cause mortality 10.7% 5.5% (*P* = 0.037)	No difference in vision, ESRD, neuropathy		Participants on study drug ~70% of time	Open label; blinded outcome assessment
5.4% 1.7% (*P* = 0.03)	All-cause mortality 8.2% 7.6% (*P* = 0.80)	Creatinine Clearance No difference	Vision NR	Participants on study drug ~70% of time	Open label; blinded outcome assessment

Table 3: Studies comparing 1 antihypertensive drug with another

Study (quality)	Study Age *y*	N groups	Blood pressure control	MI
UKPDS-39 1998[63] (Diabetics) (fair)	8.4 56	Captopril: 400 Atenolol: 358	144/83 143/81	20.2* 16.9 (*P* = 0.35)
CAPPP, 1999[76] 2001[68] (Diabetes subgroup) (fair)	6.1 55-56	Captopril: 309 Conventional: 263	155.5/89 153.5/88	3.9% 10.3% (*P* = 0.002)
STOP-2 2000[66] (Diabetes subgroup) (fair)	5.3 75-76	ACEI: 235 CA: 231 Conventional: 253 (D/ß)	161.3/80.3 161.8/79.1 161.3/81.2	15.3* 29.6 22.2 (*P* = 0.025)
ABCD 1998[64] (hypertensive) (Diabetics) (fair)	5 57	Nisoldipine: 235 Enalapril: 235	135/82 135/82	10.6% 2.1% (*P* = 0.001)
FACET 1998[67] (Diabetics) (fair)	2.5 62-63	Fosinopril: 189 Amlodipine: 191	157/88 153/86	1.8† 2.4† (*P* > 0.1)
NORDIL 2000[70] (Diabetes subgroup) (fair)	4.5 60-61	Diltiazem: 351 D/ß: 376	152.2/87.6 149.1/87.4	11.2* 11.1 (*P* = 0.99)

* events per 1,000 person - years

† events per 100 person - years

‡ MI, stroke, cardiovascular death, amputation, congestive heart failure

§ doubling of creatinine, end-stage renal disease, any death

ABCD indicates Appropriate Blood Pressure Control in Diabetes; ACEI, angiotensin converting enzyme inhibitor; CA, calcium antagonist; CAPPP, Captopril Prevention Project; CVD, cardiovascular disease; D/ß, diuretics and/or beta blockers; D/C, discontinue; DM, diabetes mellitus; ESRD, end stage renal disease; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GITS, gastrointestinal-transport-system; INSIGHT, Intervention as a Goal in Hypertension Treatment; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; MI, myocardial infarction; NORDIL, Nordic Diltiazem study; NR, not reported; NS, not statistically significant; STOP-2, Swedish Trial in Old Patients with Hypertension-2; UKPDS, UK Prospective Diabetes Study Group.

Table 3: Studies comparing 1 antihypertensive drug with another (continued)

Stroke	CVD events Mortality	Non-CVD outcomes	Adherence Withdrawal	Blinding comments
6.8* 6.1 (*P* = 0.74)	DM related death 15.2* 12.0 (*P* = 0.28)	No difference vision, ESRD	D/C study drug 22% 35%	Open label; blinded outcome assessment
7.4% 7.2% (*P* = 0.96)	All cause 6.5% 12.9% (*P* = 0.034)	NR	One patient lost to follow-up; compliance with medications not reported	Open label; blinded outcome assessment
31.6* 26.9 34.7 (*P* = 0.36)	All cause 49.0* 43.9 55.5 (*P* = 0.20)	NR	Taking drug at end ACEI : 61.3% CA: 66.2% D/ß: 62.3% 0% withdrew	Open label; blinded outcome assessment
4.7% 3.0% (NS)	CVD death 4.3% 2.1% (NS)	No difference vision, ESRD	D/C study drug: 39.1% 34.9%	Double-blind; MI a secondary endpoint; blinded outcome assessment
0.7† 1.9 (*P* > 0.1)	Major CVD event 2.6† 5.0 (*P* = 0.03)	NR	D/C study drug 19.0% 27.2% 1% withdrew	Open label; blinded outcome assessment
13.3* 12.3 (*P* = 0.97)	CVD events 29.8* 27.7 (*P* = 0.98)	NR	Taking drug at end 77% 93% <1% withdrew	Open label; blinded outcome assessment

Continued on p. 12

Table 3: Studies comparing 1 antihypertensive drug with another (continued)

Study (quality)	Study Age *y*	N groups	Blood pressure control	MI
INSIGHT 2000[69] (Diabetes subgroup) (fair)	4 65	Nifedipine: 649 (GITS) Co-amilozide: 653 (diuretic)	138/82 138/82	NR
LEWIS et al. 2001[71] (Diabetics) (good)	2.6 58-59	Irbesartan: 579 Amlodipine: 567 Placebo: 569	140/77 141/77 144/80	NR
ABCD 2002[62] (normotensive) (Diabetics) (fair)	5.3 58-59	Nisoldipine: 234 Enalapril: 246	132.1/78.0 132.4/78.0	7.7% 6.5% (*P* = 0.61)
LIFE 2002[75]; LIFE 2002[74] (Diabetes subgroup) (good)	4.7 67	Losartan: 586 Atenolol: 609	146/79 148/79	7% 8% (*P* = 0.37)

* events per 1,000 person - years

† events per 100 person - years

‡ MI, stroke, cardiovascular death, amputation, congestive heart failure

§ doubling of creatinine, end-stage renal disease, any death

ABCD indicates Appropriate Blood Pressure Control in Diabetes; ACEI, angiotensin converting enzyme inhibitor; CA, calcium antagonist; CAPPP, Captopril Prevention Project; CVD, cardiovascular disease; D/ß, diuretics and/or beta blockers; D/C, discontinue; DM, diabetes mellitus; ESRD, end stage renal disease; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GITS, gastrointestinal-transport-system; INSIGHT, Intervention as a Goal in Hypertension Treatment; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; NORDIL, Nordic Diltiazem study; NR, not reported; NS, not statistically significant; STOP-2, Swedish Trial in Old Patients with Hypertension-2; UKPDS, UK Prospective Diabetes Study Group.

Table 3: Studies comparing 1 antihypertensive drug with another (continued)

Stroke	CVD Events Mortality	Non-CVD outcomes	Adherence Withdrawal	Blinding comments
NR	CVD events 8.3% 8.4% (NS)	NR	D/C study drug 33.1% 39.9% 2.4% withdrew	Double-blind; blinded outcome assessment Randomization imbalance in diabetic subgroup
NR	CV outcome‡ 23.8% 22.6% 25.3% (NS)	Renal outcome§ 32.6% (*P* = 0.006) 41.1% 39.0% (*P* = 0.02)	<1% withdrew	Double-blind; blinded outcome assessment Randomized by central office
4.7% 2.4% (*P* = 0.18)	All cause mortality 8.1% 7.7% (*P* = 0.87)	No differences in renal and visual outcomes	Participants taking study drug ~ 70% of time	Double-blind; placebo controlled; blinded outcome assessment
9% 11% (*P* = 0.20)	All cause mortality 11% 17% (*P* = 0.002)	NR	Taking drug at end 73% 68%	Double-blind; blinded outcome assessment

Table 4: Meta-analyses of comparisons of antihypertensive drugs

Study (population) (quality)	Inclusion criteria	Number of studies
Blood Pressure Trialists 2000[72] (Diabetics and nondiabetics) (good)	Random assignment of patients between anti- hypertensive regimens minimum of 1000 P-ys in each group prespecified outcomes	8
Pahor et al. 2000[73] (Diabetics and nondiabetics) (good)	Patients with hypertension; compared CA with another drug; assessed CVD events; included 100 people or more	9
Pahor et al. 2000[65] (Diabetics only) (good)	RCT of ACE inhibitor vs other drug for hypertensive diabetics; ≥ 2 yrs follow-up; CVD outcomes	4 ABCD CAPPP FACET UKPDS (heterogeneity)

* RR (95% CI); values <1 favors calcium antagonists

† OR (95% CI); OR <1.0 favors calcium antagonists

‡ RR (95% CI); RR <1.0 favors ACE inhibitor

ACEI indicates angiotensin converting enzyme inhibitor; CA, calcium antagonists; D/ß, diuretics and/or Bblockers; p-ys, person - years; first column compares calcium antagonists with diuretic/Bblockers

Table 4: Meta-analyses of comparisons of antihypertensive drugs (continued)

Comparisons				
calcium antagonists vs		**ACE inhibitors vs**	**calcium antagonists vs**	**comments**
D/ß		D/ß	ACEI	Heterogeneity in trials comparing CA and ACEI
CHD	1.12*(1.00 - 1.26)	No difference for any outcome	1.23*(1.03 - 1.47)	
Stroke	0.87 (0.77 - 0.98)		0.98 (0.83 - 1.18)	
CHF	1.12 (0.95 - 1.33)		1.22 (1.00 - 1.49)	
CVD events	1.02 (0.95 - 1.10)		1.09 (0.99 - 1.20)	
Mortality	1.01 (0.92 - 1.11)		0.97 (0.85 - 1.10)	
All other drugs, all participants		CA, all participants	All other drugs, diabetics	Diabetics qualitatively same as all participants, but with higher ORs
MI	1.26† (1.11 - 1.43)	1.43† (1.15 - 1.76)	1.53† (1.01 - 2.31)	
Stroke	0.90 (0.80 - 1.02)	1.01 (0.84 - 1.23)	1.37 (0.86 - 2.20)	
CHF	1.25 (1.07 - 1.46)	1.24 (1.00 - 1.55)	1.76 (0.97 - 3.21)	
CVD events	1.10 (1.02 - 1.18)	1.18 (1.04 - 1.33)	1.44 (1.09 - 1.91)	
Mortality	1.03 (0.94 - 1.13)	0.97 (0.83 - 1.13)	1.24 (0.84 - 1.83)	
NA		D/ß or CA	NA	Heterogeneity when UKPDS added in; results are for other 3 trials without UKPDS
	MI	0.37‡ (0.24 - 0.57)		
	Stroke	0.76 (0.48 - 1.22)		
	CVD events	0.49 (0.36 - 0.67)		
	Mortality	0.57 (0.38 - 0.87)		

acid derivatives (fibrates) lower the risk of CHD events; relative risk reduction is similar (about 25% to 30%) in both diabetic persons and nondiabetic persons.[89-101] Aspirin also effectively reduces CHD events in both diabetic persons and nondiabetic persons with a similar relative risk reduction (about 30%).[102-106]

To determine the value of knowing about diabetes status for lipid treatment, a study would ideally randomly assign both diabetic persons and nondiabetic persons without established vascular disease to groups that differed in target LDL levels or class of drug. It could then be determined whether diabetic persons should be treated differently from other groups. No such trial has been completed.

Two other studies provide mixed evidence about this issue. A secondary analysis of two secondary prevention studies found that diabetic persons but not nondiabetic persons with LDL-C below 3.2 mmol/L (<125 mg/dL) benefited from statin treatment.[107] A recent large study of statin treatment that included diabetic persons without established vascular disease as well as nondiabetic persons with vascular disease found a similar relative risk reduction in CHD mortality for all groups, including those with initial LDL-C below 3.0 mmol/L (<116 mg/dL).[99] Thus, it is not clear whether clinicians should treat LDL-C more aggressively in diabetic persons than in nondiabetic persons. Absolute benefit may be determined by overall CHD risk rather than diabetes status itself.

Furthermore, it is not certain whether the most effective target for diabetic persons is LDL-C levels (which might lead to initial statin treatment) or HDL-C levels (which might lead to initial fibrate treatment) and whether different strategies should be used in diabetic and nondiabetic persons. Expert groups recommend that lipid and aspirin treatment be based on CHD risk; diabetes status is an important determining factor.[108] Thus, persons without previously diagnosed diabetes who would cross a threshold for initiation of aggressive treatment of lipids or aspirin in the presence of diabetes could potentially benefit from screening and earlier treatment.

The magnitude of added benefit from earlier detection of diabetes for either treatment of lipids or the use of aspirin is uncertain. If one considers that undetected diabetes increases CHD risk by a factor of two or more, and that aspirin and lipid treatment are clearly effective in reducing CHD events over 5 years, then the magnitude of this added benefit is potentially substantial.

Counseling for Diet, Physical Activity, and Smoking Cessation

For both diabetic persons and nondiabetic persons, dietary change, increased physical activity, and smoking cessation are important behavioral steps to reduce adverse health events. No study has found that counseling is more effective in changing long-term behavior for diabetic persons than for nondiabetic persons or that effective behavioral change programs for diabetic persons should be designed differently from programs for nondiabetic persons.

Foot Care Programs

Although foot care programs may decrease the risk for amputation among persons with long-standing diabetes,[109-111] no study has shown that initiation of such programs during the preclinical period provides additional benefit. Because the risk of amputation in the 10 years after clinical diagnosis is low,[112] the additional benefit from starting such programs in the preclinical phase is uncertain but likely to be small.

Does Diagnosis and Treatment of Impaired Fasting Glucose or Impaired Glucose Tolerance Improve Health Outcomes?

Impaired fasting glucose (IFG) and *impaired glucose tolerance* (IGT) are terms for conditions among persons who do not meet criteria for diabetes but whose FPG level or 2-hPG level is in the top few percentiles of the nondiabetic population.[12] These people have an increased risk for diabetes in the future but do not usually develop diabetic visual, neurological, or renal complications while in this intermediate state. People with IFG or IGT,

however, have more CVD risk factors and higher CVD risk than nondiabetics.[34-39,85,113-115] People with IFG or IGT do not have symptoms of hyperglycemia; their state can be detected only by screening. In screening studies, more than twice as many persons have IFG or IGT as have undiagnosed diabetes.[12,41]

If interventions at the stage of IFG or IGT can reduce diabetic complications, this would be a potential benefit of screening. Five RCTs have reported results from lifestyle or drug interventions in people with IFG or IGT, using progression to diabetes as the relevant outcome.[116-120] Three of these trials (the largest ones with the most intensive interventions) found that intensive lifestyle interventions reduced the development of diabetes by 42% to 58% over 3 to 6 years.[117,119,120] In the largest, U.S.-based study, for example, the intensive behavioral and social program included a case manager with frequent meetings, group and individual support, diet and physical activity training, and enrollment at an exercise facility.[121]

Although these trials convincingly demonstrate that intensive behavioral and social interventions can reduce the progression from IFG or IGT to diabetes, determining the magnitude of additional health benefit from screening and intervening at this stage rather than waiting to intervene at clinical diagnosis is complex. The trials do not permit a clear estimate of the added impact on diabetic complications. Because the risk for development of severe visual impairment, ESRD, or amputation is low until 15 years or more after diabetes diagnosis, any benefit of treatment of IFG or IGT to prevent these complications would be small for at least this period. The effect of lifestyle interventions on CVD events, independent of other risk factor modification, is also uncertain. Finally, the cost-effectiveness of offering lifestyle interventions only to persons who have positive results on a glucose screening test compared with offering these programs more generally to people with such risk factors for diabetes as obesity or sedentary lifestyle is uncertain.

What Are the Harms of Screening and Treatment, and How Frequently Do They Occur?

Screening for diabetes could potentially cause harm in several ways. One way is by labeling people as diabetic. One study in a Veterans Association Medical Center screened a convenience sample of 1,253 outpatients for diabetes, and also administered a global measure of quality of life.[122] The study found no differences in quality of life at baseline or 1 year later between patients newly detected by screening to have diabetes and those not found to have diabetes. Whether more sensitive measures in healthier samples would have similar findings is unclear. No study has examined the psychological effects of diabetes detection by screening compared with clinical detection. Because few studies have examined the harmful effects of screening, the possibility of labeling effects remains a potential harm. False-positive diagnoses may also cause unnecessary treatment, and difficulty obtaining life or health insurance. Between 30% and 50% of people receive a diagnoses of IGT will revert to normoglycemia.[123-128] Two studies found that between 12.5% and 42% of men who were found to have diabetes on screening reverted to normoglycemia after 2.5 to 8 years.[129,130]

Another potential harm of screening is subjecting people to a potentially harmful or unnecessary treatment for a longer time. On the whole, treatments for diabetes are relatively safe. Tight glycemic control, especially at a time when glycemic levels are low (ie, the time between screening and clinical detection), can induce hypoglycemia. In the UKPDS, 2.3% of people taking insulin had a major hypoglycemic episode each year, as did 0.4% to 0.6% of persons taking oral hypoglycemic agents.[10] The most common side effect of ACE inhibitors, a reversible cough, occurs in 5% to 20% of patients and is dose-related.[131] ACE inhibitors have fewer side effects than most antihypertensive agents and are associated with high rates of adherence. Statins also have low rates of serious adverse effects.[132,133]

Although the effect of tight glycemic control on quality of life has been a concern, 3 RCTs indicate that better glycemic control actually improves quality of life.[134-136] These studies were conducted in persons with a clinical diagnosis of diabetes, whose glycemic levels were presumably higher than those of persons who would be detected by screening.

Discussion

No RCT of screening for diabetes has been performed. The natural history of diabetes includes an asymptomatic preclinical phase, and currently available screening tests can detect the disease during this period. The mean length and distribution of lengths of this preclinical period are unknown. A longer preclinical period provides a better opportunity for early treatment to reduce complications.

Early detection by screening could allow clinicians to offer a variety of interventions during the preclinical period, including tight glycemic control; more intensive use and targeted choice of antihypertensive agents; more aggressive use of lipid treatment and aspirin; institution of foot care programs; and counseling for dietary change, physical activity, and smoking cessation. Direct evidence shows that many of these interventions improve health outcomes when initiated after clinical diagnosis; the magnitude of added benefit to initiating them earlier, during the preclinical period, however, must be extrapolated from indirect evidence.

The effect of earlier initiation of these interventions depends on the magnitude of the absolute risk reduction of the complications that they target. The impact of earlier initiation of interventions, such as tight glycemic control, that target blindness, ESRD, or lower extremity amputation—complications that occur in a substantial number of diabetic persons only 15 years or more after diagnosis—is uncertain but probably small for some years. By contrast, the impact of earlier initiation of interventions, such as intensive blood pressure control, that target CVD events—complications that occur sooner and at a higher rate than blindness—is likely to be larger within the first 10 years after diagnosis.

Table 5. Number needed to screen (NNS) for diabetes to prevent 1 adverse event

Tight glycemic control to prevent 1 case of blindness in 1 eye*			
Screening 1,000 persons with given prevalence			
Prevalence of undiagnosed diabetes	Addt'l time of intensive treatment due to screening	Increase in tight glycemic/ blood pressure control due to screening	Cases of blindness averted (NNS)
6%	5		
		25%	0.07 (15,400)
		50%	0.13 (7,700)
		90%	0.23 (4,300)
3%	2.5		
		25%	0.02 (61,400)
		50%	0.04 (30,700)
		90%	0.07 (17,000)

*__Assumptions:__

a) 1.5% 5-year risk of blindness in one eye with no glycemic control;[10]

b) Relative risk reduction for blindness with tight glycemic control is same as relative risk reduction for photocoagulation.[10]

Table 5 considers the number needed to screen (NNS) to prevent one case of blindness in one eye or one CVD event over five years, given various assumptions. Given favorable assumptions, including that tight glycemic control yields a 29% reduction in the risk for blindness in one eye among diabetic persons identified by screening (the relative risk reduction in retinal photocoagulation in the UKPDS trial)[10] and that screening increases the percentage of persons with tight control by 90%, then the NNS to prevent one case of blindness by tight glycemic control for 5 years is about 4,300. Less optimistic assumptions result in higher NNS estimates.

If one screened only persons with hypertension for diabetes, estimates of the NNS to prevent one CVD event with 5 years of intensive hypertension treatment are lower. Realistic assumptions of the risk for CVD events and the relative risk reduction from intensive hypertension control lead to an NNS estimate of 900 even with an increase of only 50% in the percentage of new diabetic persons with tight blood pressure control. With less favorable assumptions, the NNS calculations for preventing one CVD event are still lower than those for preventing blindness in one eye. The initial assumptions for the CVD calculations are based more on direct evidence and less on extrapolation than those in the blindness example.

Special Populations

A systematic review in 1994 found that nearly all minority groups in the United States have a higher prevalence of diabetes than white persons.[137] Many of these groups also have a higher incidence and prevalence of such diabetic complications as ESRD and higher overall mortality rates.[138] The RCTs of interventions cited in this review include predominantly white patients. Thus, the relative risk reduction for diabetic complications in minority groups must be extrapolated from data on white samples.

Assuming that the effectiveness of the interventions is similar in various ethnic groups, the most important issue from the standpoint of benefit from screening is whether the rates of development of diabetic complications in minority groups are different from those of persons in the intervention

Table 5. Number needed to screen (NNS) for diabetes to prevent 1 adverse event (continued)

Tight blood pressure control to prevent 1 cardiovascular (CVD) event†		
Screening 1,000 hypertensives‡ with given prevalence		
	Increase in persons with tight blood pressure control due to screening	CVD events averted (NNS)
Number of CVD events after 5 years	25%	0.56 (1,800)
	50%	1.13 (900)
	90%	2.03 (500)
Number of CVD events after 5 years	25%	0.14 (7,200)
	50%	0.28 (3,600)
	90%	0.51 (2,000)

†**Assumptions:**

a) 7.5% 5-year risk of CVD event with usual blood pressure control; [60]

b) 50% relative risk reduction in CVD events with tight blood pressure control.[59] Usual blood pressure control is equivalent to a diastolic goal of 90mm Hg; tight blood pressure control is having a diastolic goal of 80mm Hg.

‡Hypertension is blood pressure = 140/90.

trials. If, for example, ESRD in minority groups occurs earlier and in a larger proportion of diabetic persons than in the study populations, and if intervening earlier with tight glycemic control or more intensive blood pressure control substantially reduces the development of these complications, then screening might well be more beneficial in these groups. Unfortunately, the evidence on these issues is insufficient to draw a conclusion.

Future Research

The most important gap in our understanding of screening for diabetes is our knowledge of the added benefit of starting various interventions earlier, during the preclinical period, compared with at clinical detection. Ideally, an RCT of screening, especially in populations that are not otherwise at high CVD risk, should be considered. Mounting such a study, although expensive and difficult, could teach us much about preventing diabetic complications and could assist us in developing the most effective and efficient strategy to reduce the burden of diabetes. Because some of these complications occur many years after clinical diagnosis, this study should include long-term follow-up.

In the absence of a trial of screening, natural experiments should be examined. Areas that adopt an aggressive screening approach (eg, among American Indian groups) could be compared with areas that offer little screening. Registries of diabetic complications, including CVD events, should be established for monitoring. Because not all persons with abnormal results on glycemic tests are at equal risk for diabetic complications, studies that help define and identify high- and low-risk groups are needed to better target such interventions as screening. Until we have better evidence about its benefits, harms, and costs, the role of screening as a strategy to reduce the burden of suffering of diabetes will remain uncertain. Current evidence suggests that the benefits of screening are more likely to come from modification of CVD risk factors rather than from tight glycemic control.

Addendum

The recently reported Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[139] provides further evidence that ACE inhibitors have no special benefit, and calcium channel blockers have no special adverse effects, in diabetic persons compared with nondiabetic persons.

References

1. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care*. 2001;24:1936–40.

2. Geiss LS. Diabetes Surveillance, 1999. Centers for Disease Control and Prevention. Washington, DC: U.S. Department of Health and Human Services; 1999.

3. Economic consequences of diabetes mellitus in the U.S. in 1997. American Diabetes Association. *Diabetes Care*. 1998;21:296–309.

4. National Diabetes Data Group, ed. Diabetes in America, 2nd Edition. Bethesda, MD: Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:429–56. NIH Publication No. 95-1468.

5. National Diabetes Data Group. Diabetes in America, 2nd ed. NIH Publication No. 95-1468. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:349–400.

6. Perneger TV, Brancati FL, Whelton PK, Klag MJ. End-stage renal disease attributable to Diabetes Mellitus. *Ann Intern Med.* 1994;121:912–8.

7. Klein R, Klein BEK. Vision disorders in diabetes. In: National Diabetes Data Group, ed. Diabetes in America, 2nd ed. Bethesda, MD: National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases; 1995: 293–338. NIH publication no. 95-1468.

8. National Diabetes Data Group, ed. Diabetes in America, 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:339–48. NIH Publication No. 95-1468.

9. National Diabetes Data Group, ed. Diabetes in America, 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995: 401–28. NIH Publication No. 95-1468.

10. 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.

11. Clark CM, Fradkin JE, Hiss RG, Lorenz RA, Vinicor F, Warren-Boulton E. Promoting early diagnosis and treatment of type 2 diabetes: the National Diabetes Education Program. *JAMA*. 2000;284:363–5.

12. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care*. 1998;21:518–24.

13. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services. 2nd ed. Washington, DC: Office of Disease Prevention and Health Promotion; 1996.

14. Wareham NJ, Griffin SJ. Should we screen for type 2 diabetes? Evaluation against National Screening Committee criteria. *BMJ*. 2001;322:986–8.

15. Engelgau MM, Aubert RE, Thompson TJ, Herman WH. Screening for NIDDM in nonpregnant adults. A review of principles, screening tests, and recommendations. *Diabetes Care*. 1995;18:1606–18.

16. Harris MI, Modan M. Screening for NIDDM. Why is there no national program. *Diabetes Care*. 1994;17:440–4.

17. Marshall KG. The folly of population screening for type 2 diabetes. *CMAJ*. 1999;160:1592–3.

18. Goyder E, Irwig L. Screening for diabetes: what are we really doing? *BMJ*. 1998;317:1644–6.

19. Davidson MB. The case for screening for type 2 diabetes in selected populations. *BMJ USA*. 2001;1:297–8.

20. ACE Consensus Conference on Guidelines for Glycemic Control. American Association of Clinical Endocrinologists. *Endocr Pract*. 2002;8(Suppl 1): 5–11.

21. American Diabetes Association. Screening for diabetes. *Diabetes Care*. 2001;24:S21–4.

22. Engelgau MM, Narayan KM, Herman WH. Screening for type 2 diabetes. *Diabetes Care*. 2000;23:1563–80.

23. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(Suppl 3):21–35.

24. Harris R, Donahue K, Rathore S, Frame P, Woolf SH, Lohr KN. Screening for Type 2 Diabetes Mellitus. Systematic Evidence Review No. 19. (Prepared by the Research Triangle Institute University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011.) Rockville, MD: Agency for Healthcare Research and Quality; 2002. (Available on the AHRQ Web site at: www.ahrq.gov/clinic/serfiles.htm.)

25. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care*. 1992;15:815–9.

26. Jarrett RJ. Duration of non-insulin-dependent diabetes and development of retinopathy: analysis of possible risk factors. *Diabet Med*. 1986;3:261–63.

27. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–97.

28. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–53.

29. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2001;24:S5–20.

30. Davidson MB, Schriger DL, Peters AL, Lorber B. Relationship between fasting plasma glucose and glyosylated hemoglobin: potential for false positive diagnoses of type 2 diabetes using new diagnostic criteria. *JAMA*. 1999;281:1203–10.

31. Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE. Use of GHb (HbA1c) in

screening for undiagnosed diabetes in the U.S. population. *Diabetes Care*. 2000;23:187–91.

32. Peters AL, Davidson MB, Schriger DL, Hasselblad V. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. *JAMA*. 1996;276:1246–52.

33. Barr RG, Nathan DM, Meigs JB, Singer DE. Tests of glycemia for the diagnosis of type 2 diabetes mellitus. *Ann Intern Med*. 2002;137:263–72.

34. Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med*. 1998;128:524–33.

35. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22: 233–40.

36. Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E. Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care*. 1999;22:45–9.

37. Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? *Diabetes Care*. 1999;22:696–9.

38. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care*. 2001;24:447–53.

39. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15–8.

40. Blunt BA, Barrett-Connor E, Wingard DL. Evaluation of fasting plasma glucose as screening test for NIDDM in older adults. Rancho Bernardo Study. *Diabetes Care*. 1991;14:989–93.

41. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care*. 1997;20:1859–62.

42. Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC, Muggeo M. Plasma glucose levels throughout the day and HbA(1c) interrelationships in type 2 diabetes: implications for treatment and monitoring of metabolic control. *Diabetes Care*. 2001;24:2023–9.

43. Olefsky JM, Reaven GM. Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes*. 1974;23:449–53.

44. Ollerton RL, Playle R, Ahmed K, Dunstan FD, Luzio SD, Owens DR. Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. *Diabetes Care*. 1999;22:394–8.

45. Mooy JM, Grootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia*. 1996;39:298–305.

46. Rolka DB, Narayan KM, Thompson TJ, Goldman D, Lindenmayer J, Alich K, Bacall D, Benjamin EM, Lamb B, Stuart DO, et al. Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care*. 2001;24:1899–903.

47. UKPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study Group. *Lancet*. 1998;352:854–65.

48. Knatterud GL, Meinert CL, Klimt CR, Osborne RK, Martin DB. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. IV. A preliminary report on phenoformin results. *JAMA*. 1971;217:777–84.

49. Knatterud GL, Klimt CR, Levin ME, Jacobson ME, Goldner MG. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII. Mortality and selected nonfatal events with insulin treatment. *JAMA*. 1978;240:37–42.

50. Azad N, Emanuele NV, Abraira C, Henderson WG, Colwell J, Levin SR, Nuttall FQ, Comstock JP,

Sawin CT, Silbert C, et al. The effects of intensive glycemic control on neuropathy in the VA cooperative study on type II diabetes mellitus (VA CSDM). *J Diabetes Complications*. 1999;13:307–13.

51. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23(Suppl 2):B21–9.

52. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS. 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;157:181–8.

53. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet*. 1999;353:617–22.

54. Emanuele N, Klein R, Abraira C, Colwell J, Comstock J, Henderson WG, Levin S, Nuttall F, Sawin C, Silbert C, et al. Evaluations of retinopathy in the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM). A feasibility study. *Diabetes Care*. 1996;19:1375–81.

55. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. 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;28:103–17.

56. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, Emanuele NV, Levin SR, Henderson W, Lee HS. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care*. 1995;18:1113–23.

57. Levin SR, Coburn JW, Abraira C, Henderson WG, Colwell JA, Emanuele NV, Nuttall FQ, Sawin CT, Comstock JP, Silbert CK. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. *Diabetes Care*. 2000;23:1478–85.

58. Ewart RM. The case against aggressive treatment of type 2 diabetes: critique of the UK prospective diabetes study. *BMJ*. 2001;323:854–8.

59. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. 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;351:1755–62.

60. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703–13.

61. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care*. 2000;23(Suppl 2):B54–64.

62. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int*. 2002;61:1086–97.

63. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:713–20.

64. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med*. 1998;338:645–52.

65. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care*. 2000;23:888–92.

66. Lindholm LH, Hansson L, Ekbom T, Dahlof B, Lanke J, Linjer E, Schersten B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens*. 2000;18:1671–5.

67. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care*. 1998;21:597–603.

68. Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care*. 2001;24:2091–6.

69. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet*. 2000;356:366–72.

70. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlof B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000;356:359–65.

71. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–60.

72. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2000;356:1955–64.

73. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Cavazzini C, Furberg CD. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet*. 2000;356:1949–54.

74. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, et al. 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.

75. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.

76. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, 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;353:611–6.

77. Schnack C, Hoffmann W, Hopmeier P, Schernthaner G. Renal and metabolic effects of 1-year treatment with ramipril or atenolol in NIDDM patients with microalbuminuria. *Diabetologia*. 1996;39:1611–6.

78. Fogari R, Zoppi A, Corradi L, Mugellini A, Lazzari P, Preti P, Lusardi P. Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. *J Hum Hypertens*. 1999;13:47–53.

79. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000;355:253–9.

80. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–8.

81. Chan JC, Ko GT, Leung DH, Cheung RC, Cheung MY, So WY, Swaminathan R, Nicholls MG, Critchley JA, Cockram CS. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney Int*. 2000;57:590–600.

82. Lovell HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. Cochrane Database Syst Review). In: *The Cochrane Library*, Issue 2, 2000. Oxford: Update Software.

83. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–9.

84. Hostetter TH. Prevention of end-stage renal disease due to type 2 diabetes. *N Engl J Med*. 2001;345:910–2.

85. Barzilay JI, Spiekerman CF, Kuller LH, Burke GL, Bittner V, Gottdiener JS, Brancati FL, Orchard TJ, O'Leary DH, Savage PJ. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care*. 2001;24:1233–9.

86. Resnick HE, Harris MI, Brock DB, Harris TB. American Diabetes Association diabetes diagnostic criteria, advancing age, and cardiovascular disease risk profiles: results from the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2000;23:176–80.

87. Saito I, Folsom AR, Brancati FL, Duncan BB, Chambless LE, McGovern PG. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Intern Med*. 2000;133:81–91.

88. Fonseca VA. Risk factors for coronary heart disease in diabetes. *Ann Intern Med*. 2000;133:154–6.

89. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastiatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care*. 1997;20:614–20.

90. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care*. 1992;15:820–5.

91. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med*. 1987;317:1237–45.

92. 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;339:1349–57.

93. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AMJr. 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;279:1615–22.

94. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–89.

95. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, 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;341:410–8.

96. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999;159:2661–7.

97. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585–91.

98. Pignone MP, Phillips CJ, Atkins D, Teutsch SM, Mulrow CD, Lohr KN. Screening and treating adults for lipid disorders. *Am J Prev Med*. 2001;20(Suppl 3):77–89.

99. 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.

100. Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, Richmond W, Mather H, Sharp P, Feher MD. 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;21:641–8.

101. Goldberg RB, Mellies MJ, Sacks FM, MoyÈ LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with Pravastatin in diabetic and glucose-intolerant myodardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) Trial. The CARE Investigators. *Circulation*. 1998;98:2513–19.

102. Colwell JA. Aspirin therapy in diabetes. *Diabetes Care*. 1997;20:1767–71.

103. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2002;136:161–72.

104. American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care*. 2001;24:S62–3.

105. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *JAMA*. 1992;268:1292–300.

106. 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.

107. Sacks FM, Tonkin AM, Craven T, Pfeffer MA, Shepherd J, Keech A, Furberg CD, Braunwald E. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. *Circulation*. 2002;105:1424–8.

108. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.

109. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. *Diabet Med*. 1998;15:80–4.

110. Litzelman DK, Slemenda CW, Langefeld CD, Hays LM, Welch MA, Bild DE, Ford ES, Vinicor F. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1993;119:36–41.

111. Patout CA Jr, Birke JA, Horswell R, Williams D, Cerise FP. Effectiveness of a comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African-American population. *Diabetes Care*. 2000;23:1339–42.

112. Resnick HE, Valsania P, Phillips CL. Diabetes mellitus and nontraumatic lower extremity amputation in black and white Americans: The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971–1992. *Arch Intern Med*. 1999;159:2470–275.

113. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;263:2893–8.

114. McPhillips JB, Barrett-Connor E, Wingard DL. Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. *Am J Epidemiol*. 1990;131:443–53.

115. Harris MI, Eastman RC. Is there a glycemic threshold for mortality risk? *Diabetes Care*. 1998;21:331–3.

116. Dyson PA, Hammersley MS, Morris RJ, Holman RR, Turner RC. The Fasting Hyperglycaemia Study: II. Randomized controlled trial of reinforced healthy-living advice in subjects with increased but not diabetic fasting plasma glucose. *Metabolism*. 1997;46:50–5.

117. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537–44.

118. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072–7.

119. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.

120. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–50.

121. The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623–34.

122. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Impact of diabetes screening on quality of life. *Diabetes Care*. 2002;25:1022–6.

123. Warram JH, Sigal RJ, Martin BC, Krolewski AS, Soeldner JS. Natural history of impaired glucose tolerance: follow-up at Joslin Clinic. *Diabet Med*. 1996;13:S40–S45

124. Yudkin JS, Alberti KG, McLarty DG, Swai AB. Impaired glucose tolerance. *BMJ*. 1990;301:397–401.

125. Balkau B, Eschwege E. Repeatability of the oral glucose tolerance test for the diagnosis of impaired glucose tolerance and diabetes mellitus. *Diabetologia*. 1991;34:201–2.

126. Eriksson KF, Lindg‰rde F. Impaired glucose tolerance in a middle-aged male urban population: a new approach for identifying high-risk cases. *Diabetologia*. 1990;33:526–31.

127. Swai AB, McLarty DG, Kitange HM, Kilima PM, Masuki G, Mtinangi BI, et al. KGMM. Study in Tanzania of impaired glucose tolerance: methodological myth? *Diabetes*. 1991;40:516–20.

128. Bourn DM, Williams SM, Mann JI. Distinguishing between persistent and transient impaired glucose tolerance using a prediction model. *Diabet Med*. 1992;9:744–8.

129. Burke JP, Haffner SM, Gaskill SP, Williams KL, Stern MP. Reversion from type 2 diabetes to nondiabetic status. Influence of the 1997 American Diabetes Association criteria. *Diabetes Care*. 1998;21:1266–70.

130. Eschwege E, Charles MA, Simon D, Thibult N, Balkau B. Reproducibility of the diagnosis of diabetes over a 30-month follow-up: the Paris Prospective Study. *Diabetes Care*. 2001;24:1941–4.

131. Israili ZH, Wall WD. Cough and angioneurotic edema associated with angiotensin-coverting-enzyme inhibitor therapy: a review of the literature and pathophysiology. *Ann Intern Med*. 1992;117:234–42.

132. Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, Higgins J, Langendorfer A, Nash DT, Pool JL, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up. *Am J Cardiol*. 1994;74:667–73.

133. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA*. 1990;264:71–5.

134. 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). U.K. Prospective Diabetes Study Group. *Diabetes Care*. 1999;22:1125–36.

135. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA*. 1998;280:1490–6.

136. Testa MA, Simonson DC, Turner RR. Valuing quality of life and improvements in glycemic control in people with type 2 diabetes. *Diabetes Care*. 1998;21(Suppl 3):C44–52.

137. Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. *Ann Intern Med*. 1996;125:221–32.

138. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. *JAMA*. 2002;287:2519–27.

139. Major outcomes in high-risk hypertensive patients randomized to angiotensin-coverting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981–2997.

Appendix

Methods

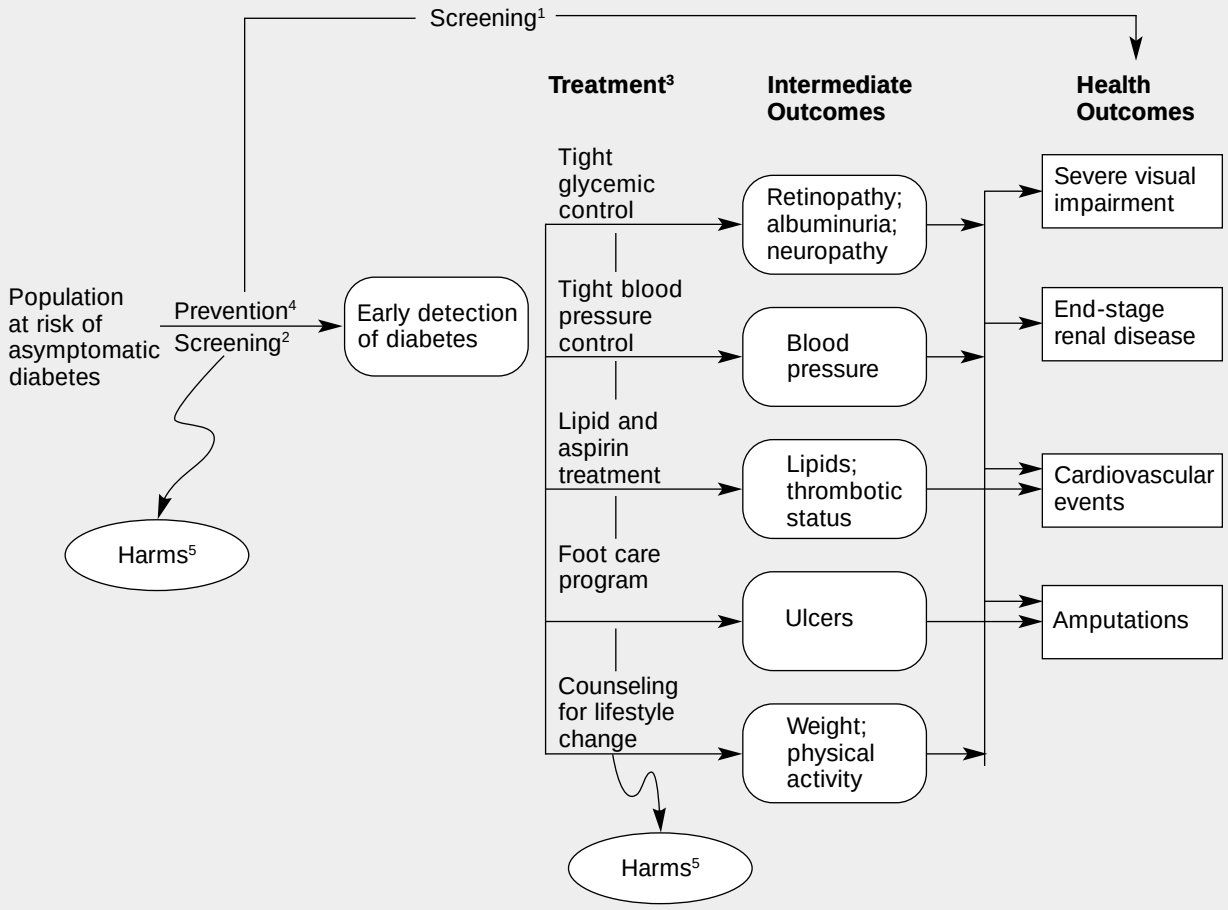
The Research Triangle Institute–University of North Carolina Evidence-based Practice Center (EPC), together with members of the US Preventive Services Task Force (USPSTF), sought to clarify issues concerning screening adults for type 2 diabetes by performing a systematic review of the relevant scientific literature on this topic.

Analytic Framework

The systematic evidence review examines the evidence for screening for diabetes, comparing systematic screening with no screening. Appendix Figure 1 presents the analytic framework that we used to guide our literature search.

The analytic framework describes the logical chain that evidence must support to link screening to improved health outcomes. Each arrow in the

Appendix Figure 1. Analytic framework: screening for type 2 diabetes



Note: Superscripts refer to Key Questions addressed by this review (see table and text).

analytic framework represents a "Key Question." We searched systematically for evidence concerning each key question in the analytic framework.

The analytic framework begins on the left side of the figure with a sample at risk of undiagnosed diabetes and moves to the right. The first Key Question (represented by the overarching arrow) examines direct evidence that screening improves health outcomes. Because no such studies were found, we continued to examine the indirect evidence in the following Key Questions, represented as linkages in the analytic framework.

Key Question 2 examines the yield of screening, involving both the accuracy and reliability of various screening tests as well as the prevalence of undiagnosed diabetes in the population. Farther to the right in the analytic framework, the third Key Question examines the efficacy of various treatments to prevent diabetic complications, including tight glycemic control, cardiovascular risk reduction, foot care, or enhanced counseling for lifestyle changes. It is important to note that the critical issue here is the efficacy of the treatment among persons who would be detected by screening. Some studies examine treatment for people with new clinically-detected diabetes; these are only useful insofar as they allow extrapolation to the efficacy of treatment at screening detection. In addition, Key Question 3 actually implies that the issue of interest is the *added* efficacy of initiating treatment after screening detection as opposed to initiation after clinical detection. An additional treatment (Key Question 4) is lifestyle intervention programs for persons with impaired fasting glucose or impaired glucose tolerance. These interventions may reduce the intermediate outcome of developing diabetes, but the critical question is the extent to which they improve health outcomes.

In between the treatment arrows and health outcomes are a variety of "intermediate outcomes," such as retinopathy and albuminuria. Although changes in these outcomes may herald later improved health outcomes, they may or may not be sufficient in themselves to allow estimation of the magnitude of health benefit with reasonable certainty.

At the far right in the analytic framework are the health outcomes—the outcomes that people can experience and care about. These include the major diabetic complications: severe visual impairment, ESRD, lower extremity amputation, and cardiovascular events. In the end, the indirect evidence must allow a reasonable estimation of the magnitude of benefit in these outcomes attributable to screening. At the bottom of the analytic framework is linkage and key question 5, the issue of the harms of screening (eg, labeling) or harms of treatment (eg, side effects).

Key Questions

Key Question 1: Is there direct evidence from an RTC of screening that screening for diabetes improves health outcomes?

Key Question 2: What is the yield of screening, both in terms of the accuracy and reliability of screening tests and the prevalence of undiagnosed diabetes in the population?

Key Question 3: What is the added efficacy of initiating treatments (tight glycemic control, tight blood pressure control, lipid and aspirin treatment, foot care programs, counseling for lifestyle change) at screening detection compared with clinical detection in improving health outcomes?

Key Question 4: What is the efficacy of lifestyle intervention for people with impaired fasting glucose or impaired glucose tolerance in improving health outcomes?

Key Question 5: What are the harms of screening or treatment?

Eligibility Criteria for Admissible Evidence

The EPC staff and USPSTF liaisons developed eligibility criteria for selecting the evidence relevant to answer the key questions (Appendix Table 1). For Key Question 1, we required a well-conducted RCT of screening of adequate size and length to estimate health outcomes with reasonable accuracy. For Key Question 2, we required cross sectional or cohort studies in which screening tests were performed on a

Appendix Table 1.
Eligibility criteria, search strategy and results of searches

Key question	Eligibility criteria	Number of articles identified for abstract review	Meeting criteria
All	**Published 1/1/94–7/30/02** **English Language** **MEDLINE, Cochrane** **Human subjects**		
1. Efficacy of screening (direct evidence)	RCT of screening	130	0
2. Accuracy and reliability of screening tests	Population relevant to primary care Screening test offered to all Screening test compared with a valid reference standard, including all positive tests and at least a sample of negatives	487	7
3. Efficacy of knowledge of diabetes status for optimizing the following treatments:			
Tight glycemic control		436	5
Tight blood pressure control; Type of drug	RCT Follow-up ≥ 2 years	426	13
Lipid and aspirin treatment	≥ 75% of patients followed	191	8
Foot care programs	Health outcomes	48	2
Counseling for lifestyle change		6	0
4. Lifestyle intervention for people with impaired fasting glucose/ impaired glucose tolerance	RCT Intervention at impaired fasting glucose/ impaired glucose tolerance stage Valid measure of development of diabetes	39	8
5. Harms of screening and treatment	Use of valid measurement instrument Follow-up for at least 12 months during treatment Comparison with similar untreated or unscreened control group	57	6

primary care or general unselected sample and compared with an acceptable reference standard. For Key Question 3, we accepted RCTs of treatments with health outcomes that provided information about disease duration and co-morbid conditions in persons with diabetes. For Key Question 4, we accepted RCTs of people with IFG or IGT treated with lifestyle or other interventions in which diabetes incidence or development of diabetic complications was an outcome. For Key Question 5, we required RCTs of screened (or treated) versus nonscreened (or nontreated) samples. When we could not find such studies, we also examined cohort studies of screening-detected diabetics for evidence of quality of life or psychosocial harms.

Literature Search Strategy, Results, and Review of Abstracts and Articles

The analytic framework and Key Questions guided our literature searches. We examined the critical literature described in the previous review of this topic by the USPSTF (published in 1996) and used our eligibility criteria to develop search terms. We used the search terms to search

MEDLINE and the Cochrane Library for English-language articles that met inclusion criteria and were published between January 1, 1994, and July 30, 2002. We also examined the bibliographies of pertinent articles and contacted experts for other references. When we found that a key question could best be answered by older literature, we also examined these studies. The search strategies are given in Appendix Table 2. All searches started with the term *noninsulin dependent diabetes*, and other terms were added as appropriate.

The first author and at least one other co-author or trained assistant reviewed all abstracts found through our searches to find those that met eligibility criteria. When either reviewer thought that an abstract might meet criteria, the article was copied for full review. The first author and at least one other co-author or trained assistant reviewed each full article. Those that met eligibility criteria after full review and, when necessary, discussion, were abstracted. Appendix Figures 2 through 6 illustrate our selection process for each key question. We critically appraised each study using criteria developed by the USPSTF Methods Work Group. If we found an article that met criteria but had methodologically fatal flaws that invalidated its findings, it was excluded from further review. Abstracted articles that met eligibility criteria and had no fatal flaws were entered into predesigned evidence tables (see Appendix B in the Systematic Evidence Review (SER), "Screening for Type 2 Diabetes Mellitis," on the AHRQ Web site at [www.preventiveservices.ahrq.gov]).

Development of the Systematic Evidence Review and Review of the Evidence Article

The authors presented an initial work plan including a provisional analytic framework and Key Questions to the entire Task Force. Interim reports were presented at subsequent meetings. The Task Force discussed and made important contributions to the review on several occasions. The 2 Task Force liaisons participated in every phase of the review, including multiple conference calls to discuss critical parts of the evidence.

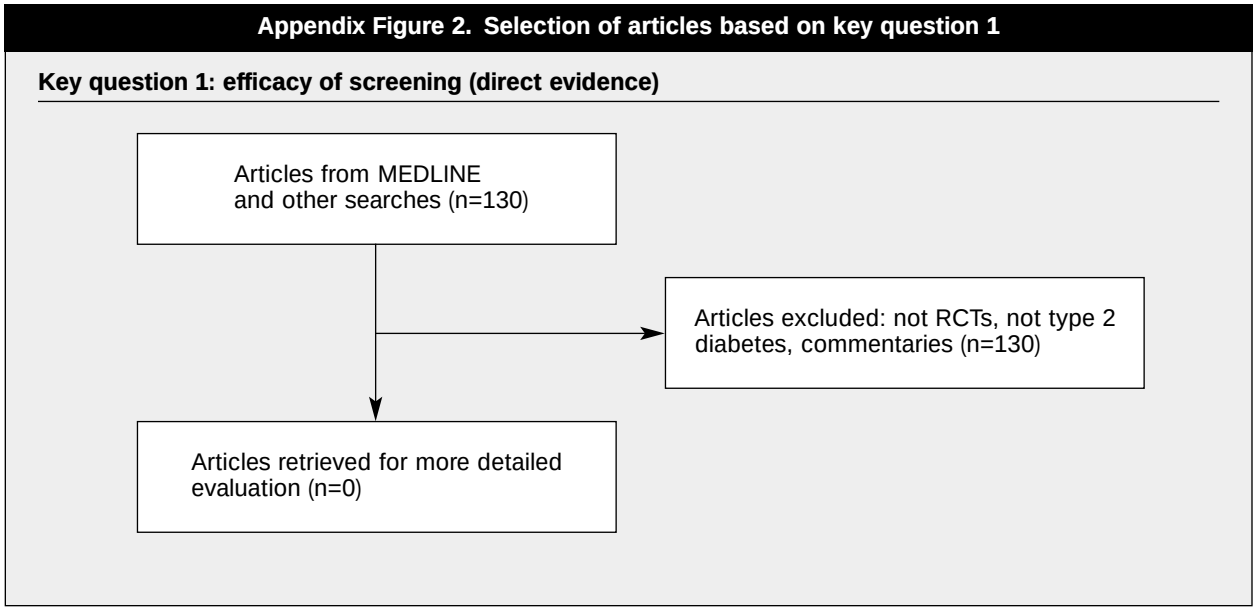
A draft systematic evidence review was presented to the Task Force and then sent for broad peer review. The peer review included individual experts in the field, representatives of relevant professional organizations, and representatives of appropriate federal agencies. We made revisions to the evidence review as appropriate after receiving peer review comments. The Task Force reviewed all information and voted on a recommendation. We then finalized the systematic evidence review for publication by the Agency for Healthcare Research and Quality and separately adapted it for journal publication.

Appendix Table 2. Search strategies

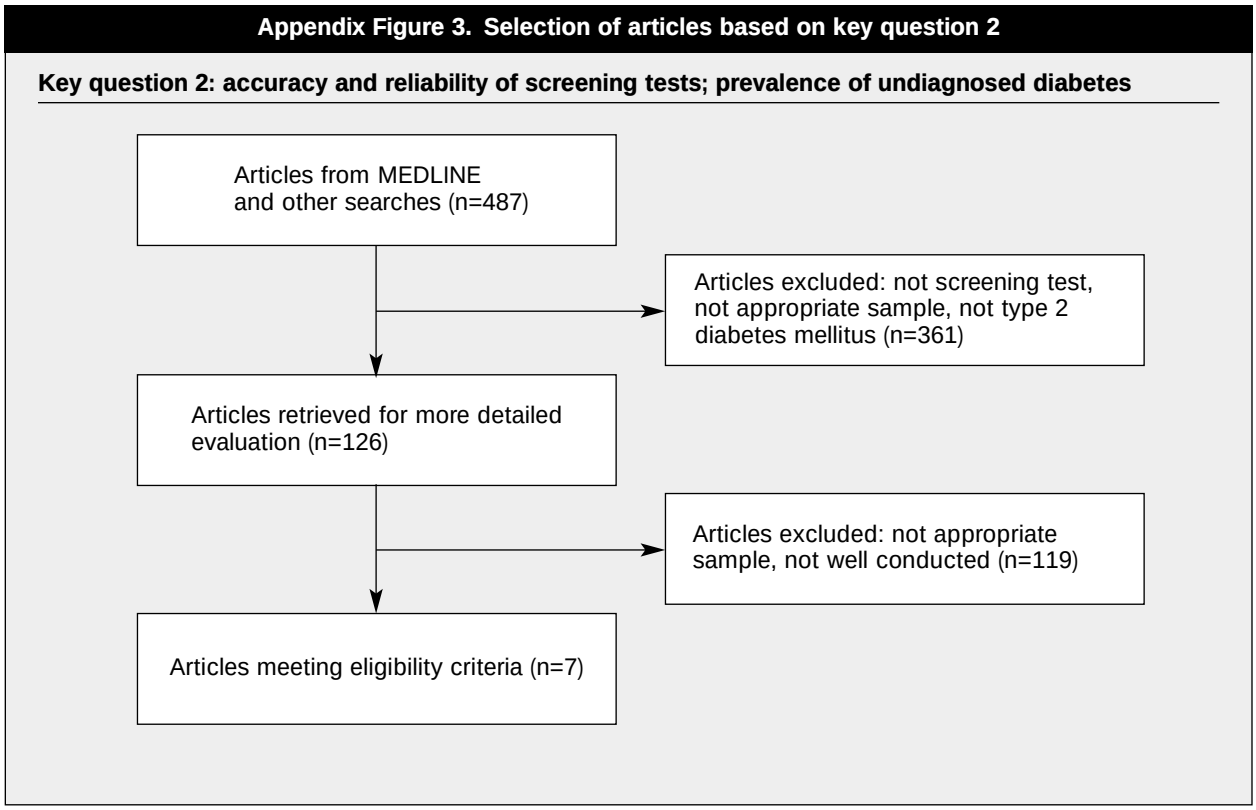
Key question	Search strategy
1: Is there direct evidence from a randomized controlled trial (RCT) of screening that screening for diabetes improves health outcomes?	NIDDM Mass screening RCT
2: What is the yield of screening?	NIDDM Prevalence, incidence Fasting glucose Random glucose Post-load glucose Glucose tolerance test Mass screening Hemoglobin AIC Glycosylated hemoglobin Diagnosis Sensitivity/Specificity Predictive value Reproducibility Screening programs
3: What is the added efficacy of initiating the treatments below at screening detection compared with clinical detection in improving health outcomes? • tight glycemic control • tight blood pressure control • lipid and aspirin treatment • foot care programs • counseling for lifestyle change	NIDDM Insulin Glycemic control Antihypertensives ACE inhibitors Calcium channel blockers Statins Aspirin Counseling Smoking Tobacco Weight change Physical activity Oral hypoglycemics Foot care programs Therapeutics Treatment
4: What is the efficacy of lifestyle intervention for people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) in improving health outcomes?	NIDDM RCT Primary prevention Impaired glucose tolerance/ Impaired fasting glucose
5: What are the harms of screening or treatment?	Therapeutics Treatment NIDDM Mass screening Labeling Hypoglycemia Adverse effects Side effects Quality of life False positive False negative Predictive value

NIDDM indicates noninsulin dependent diabetes mellitus

Appendix Figure 2. Selection of articles based on key question 1

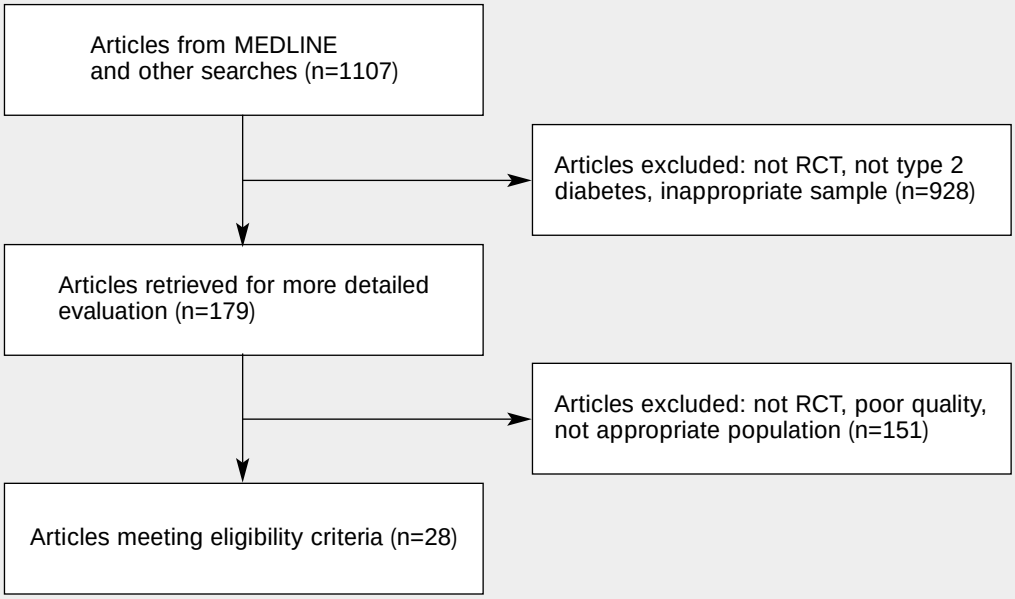


Appendix Figure 3. Selection of articles based on key question 2



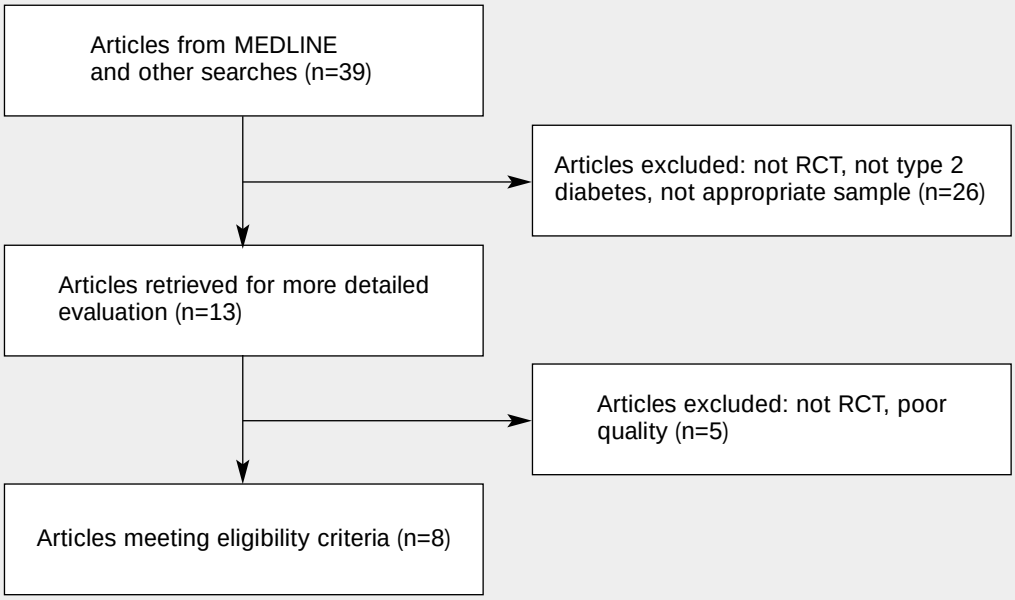
Appendix Figure 4. Selection of articles based on key question 3

Key question 3: efficacy of treatment



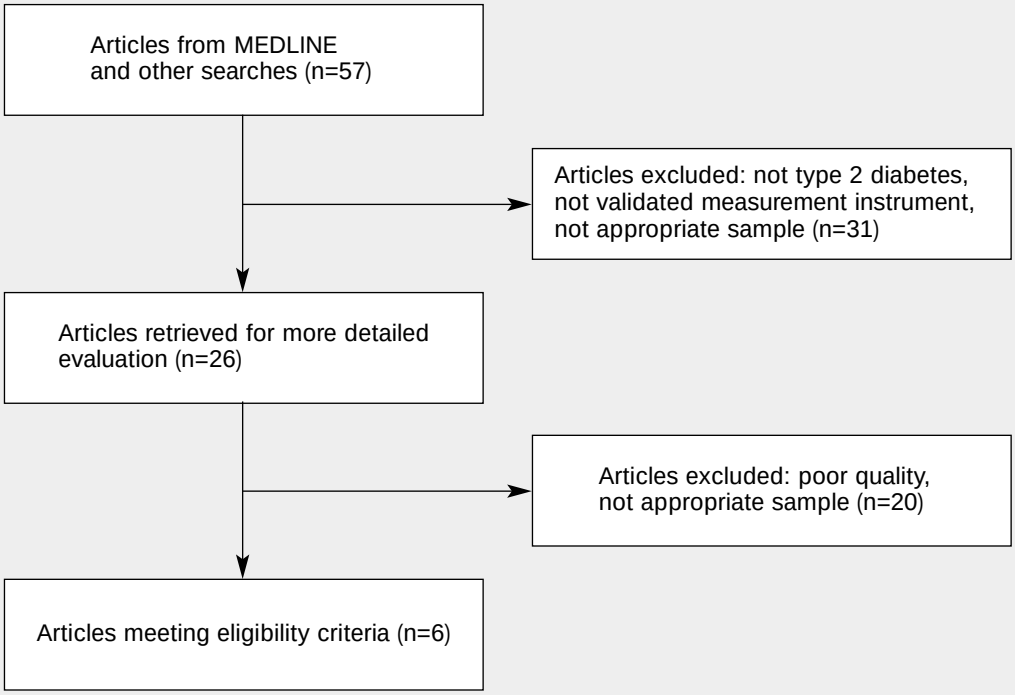
Appendix Figure 5. Selection of articles based on key question 4

Key question 4: lifestyle interventions for people with impaired fasting glucose or impaired glucose tolerance



Appendix Figure 6. Selection of articles based on key question 5

Key question 5: harms of screening or treatment



AHRQ Pub. No. 03-517B
January 2003