

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

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## Epidemiology

The prevalence of type 2 diabetes mellitus (diabetes) in the United States is growing<sup>1,2</sup>; the burden of suffering caused by its complications is heavy<sup>3</sup> and may also be growing. These complications include increased risk of cardiovascular disease (CVD),<sup>4</sup> end-stage renal disease (ESRD),<sup>5,6</sup> blindness,<sup>7</sup> and amputation of the lower extremities.<sup>8,9</sup> 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.<sup>10</sup>

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.<sup>11</sup> 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.<sup>12</sup> In 1996, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against screening for diabetes.<sup>13</sup> Since that USPSTF review, new evidence concerning the effectiveness of various treatments to prevent complications has fueled

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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.<sup>14-22</sup> 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.<sup>23</sup> 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.<sup>23</sup> 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](http://www.ahrq.gov)).<sup>24</sup> 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%.<sup>12</sup> 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<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30-32</sup>

It is not clear which of these tests and cutpoints most closely predicts diabetic complications.<sup>33</sup> The cut-point for the 2-hPG test was based on a threshold that predicted retinopathy prevalence in several studies.<sup>27,28</sup> The FPG cutpoint was chosen to correspond to that for the 2-hPG test.<sup>27,28</sup> 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.<sup>34-39</sup> 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.<sup>40</sup> 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%.<sup>41</sup> HbA1c level is more closely related to FPG than to 2-hPG level,<sup>42</sup> but it is not sensitive to low levels of hyperglycemia.<sup>30</sup> Reliability is higher for FPG than for HbA1c or 2-hPG level.<sup>43-45</sup> Although the reliability of the HbA1c assay has been a concern, it is not as grave a problem.<sup>43</sup>

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.<sup>46</sup>

## 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).<sup>10,47-57</sup> Four of these studies,<sup>48-56</sup> 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.<sup>10</sup> Because the UKPDS intervention was not blinded, outcomes that involve clinician judgment (such as whether to use retinal photocoagulation) could have been biased.<sup>58</sup>

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 <sup>48</sup> 1978 <sup>49</sup> (fair)	8.75	Placebo: n = 204 Insulin variable: n = 198	22.8% increase* 13.5% decrease*	NR
UKPDS 33 1998 <sup>10</sup> (good)	10	Conventional therapy: n = 1,138 Intensive therapy: n = 2,729	7.9%† 7.0%†	< 1% < 1% (P = 0.45)
UKPDS 34 1998 <sup>47</sup> (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 <sup>55</sup> 2000 <sup>51</sup> (fair)	8	Conventional therapy: n = 50 Intensive therapy: n = 52	9.4%† 7.1%†	NR
VA CSDM 1997 <sup>52</sup> 1996 <sup>54</sup> 1995 <sup>56</sup> 1999 <sup>50</sup> 2000 <sup>57</sup> (fair)	2.25	Standard therapy: n = 78 Intensive therapy n = 75	9.2%† 7.1%†	NR
Steno 2, 1999 <sup>53</sup> (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
<u>Acuity = 20/200 either eye</u> 11.2% 11.4% (NS)	<u>Significant ECG abnormality</u> 20% 17.6% (NS)	NR	1.5% 1.6% (NS)	26.3% 24.0% (NS)
<u>Vision too poor to drive</u> 11%  11% (NS)	16.3%  14.2% (P = 0.052)	4.8%  5.4% (P = 0.052)	1.6%  1.0% (P = 0.099)	18.7%  17.9% (P = 0.044)
<u>Blind in one eye</u> 3.2%  3.5% (P = 0.87)	17.8%  11.4% (P = 0.001)	5.6%  3.5% (P = 0.13)	2.2%  1.8% (P = 0.57)	21.7%  14.6% (P = 0.011)
NR	<u>Major CVD event</u> 1.3 events/100 P-y  0.6 events/100 P-y NS			NR
<u>Unilateral or bilateral visual impairment</u> 9.0%  6.7% (NS)	5.1%  6.7% (NS)	2.6%  6.7% (NS)	0  1.3% (NS)	5.1%  6.7% (NS)
<u>Blind in one eye</u> 9.0% 1.3% (P = 0.03)	<u>Nonfatal</u> 5.1%  5.2% (NS)	<u>Nonfatal</u> 10.2%  1.3% (NS)	5.1%  5.2% (NS)	2.6%  5.2% (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.<sup>10</sup> 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.<sup>48,49,51,52,56</sup> The most positive study, a UKPDS analysis, had puzzling results.<sup>47</sup> 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.<sup>47</sup>

In three of the studies, tight glycemic control reduced the progression of albuminuria and retinopathy.<sup>10,51,57</sup> 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<sup>53</sup> 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<sup>10,49</sup>; 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).<sup>59</sup> 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).<sup>60-62</sup>

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<sup>62-76</sup> (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.<sup>73</sup>

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).<sup>62-64,66-68,74-76</sup> 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.<sup>75</sup> ACE inhibitors or ARBs also reduce the development of diabetic nephropathy<sup>77-82</sup> and its progression to ESRD<sup>71,83,84</sup> 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<sup>63</sup>; another study of normotensive diabetics found no difference in outcomes between treatment with an ACE inhibitor compared with a CA (Table 3).<sup>62</sup> 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,<sup>68,72,74-76</sup> 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).<sup>72</sup> (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.<sup>34-39,85</sup> 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).<sup>86</sup> They may also have a tendency toward thrombosis.<sup>87,88</sup> 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 <sup>60</sup> (fair) Patients with diabetes and hypertension	<u>8.4</u> 56-57	Less tight blood pressure control: 390 Tight: 758	154/87  144/82	23.5*  18.6 ( <i>P</i> = 0.13)
HOT, 1998 <sup>59</sup> Diabetes subgroup (fair)	<u>3.8</u> 61.5	Target DBP ≤90†: 501 ≤85: 501 ≥80: 499	143.7/85.2 141.4/83.2 139.7/81.1	7.5* 4.3 3.7 ( <i>P</i> = 0.11)
ABCD, 2000 <sup>61</sup> Patients with hypertension and diabetes (fair)	<u>5</u> 57	Moderate blood pressure control: 233 Intensive: 237	138/86 132/78	No difference
ABCD 2002 <sup>62</sup> Normotensive patients with diabetes (fair)	<u>5.35</u> 58-59	Moderate blood pressure control: 243 Intensive: 237	137/81 128/75	6.2% 8.0% ( <i>P</i> = 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*	<u>DM mortality</u> 20.3*	<u>ESRD</u> 2.3*	<u>Vision</u> 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
	<u>CVD mortality*</u>			<u>%DBP &gt; 90 mmHg</u>	Open label; blinded outcome assessment
9.1*	11.1*	NR		12%	
7.0	11.2			7%	
6.4 (P = 0.34)	3.7 (P = 0.016)			6% 2.6% study withdrawal	
No difference	<u>All-cause mortality</u> 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%	<u>All-cause mortality</u> 8.2%	<u>Creatinine Clearance</u>	<u>Vision</u> NR	Participants on study drug ~70% of time	Open label; blinded outcome assessment
1.7% (P = 0.03)	7.6% (P = 0.80)	No difference			

Table 3: Studies comparing 1 antihypertensive drug with another

Study (quality)	Study Age y	N groups	Blood pressure control	MI
UKPDS-39 1998 <sup>63</sup> (Diabetics) (fair)	<u>8.4</u> 56	Captopril: 400 Atenolol: 358	144/83 143/81	20.2* 16.9 ( <i>P</i> = 0.35)
CAPPP, 1999 <sup>76</sup> 2001 <sup>68</sup> (Diabetes subgroup) (fair)	<u>6.1</u> 55-56	Captopril: 309 Conventional: 263	155.5/89 153.5/88	3.9% 10.3% ( <i>P</i> = 0.002)
STOP-2 2000 <sup>66</sup> (Diabetes subgroup) (fair)	<u>5.3</u> 75-76	ACEI: 235 CA: 231 Conventional: 253 (D/B)	161.3/80.3 161.8/79.1 161.3/81.2	15.3* 29.6 22.2 ( <i>P</i> = 0.025)
ABCD 1998 <sup>64</sup> (hypertensive) (Diabetics) (fair)	<u>5</u> 57	Nisoldipine: 235 Enalapril: 235	135/82 135/82	10.6% 2.1% ( <i>P</i> = 0.001)
FACET 1998 <sup>67</sup> (Diabetics) (fair)	<u>2.5</u> 62-63	Fosinopril: 189 Amlodipine: 191	157/88 153/86	1.8† 2.4† ( <i>P</i> > 0.1)
NORDIL 2000 <sup>70</sup> (Diabetes subgroup) (fair)	<u>4.5</u> 60-61	Diltiazem: 351 D/B: 376	152.2/87.6 149.1/87.4	11.2* 11.1 ( <i>P</i> = 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/B, 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	Blinding comments
			Withdrawal	
6.8* 6.1 (P = 0.74)	<u>DM related death</u> 15.2* 12.0 (P = 0.28)	No difference vision, ESRD	<u>D/C study drug</u> 22% 35%	Open label; blinded outcome assessment
7.4% 7.2% (P = 0.96)	<u>All cause</u> 6.5% 12.9% (P = 0.034)	NR	One patient lost to follow-up; compliance with medications not reported	Open label; blinded outcome assessment
31.6* 26.9 34.7 (P = 0.36)	<u>All cause</u> 49.0* 43.9 55.5 (P = 0.20)	NR	<u>Taking drug at end</u> ACEI : 61.3% CA: 66.2% D/B: 62.3%  0% withdrew	Open label; blinded outcome assessment
4.7% 3.0% (NS)	<u>CVD death</u> 4.3% 2.1% (NS)	No difference vision, ESRD	<u>D/C study drug:</u> 39.1% 34.9%	Double-blind; MI a secondary endpoint; blinded outcome assessment
0.7† 1.9 (P > 0.1)	<u>Major CVD event</u> 2.6† 5.0 (P = 0.03)	NR	<u>D/C study drug</u> 19.0% <u>27.2%</u>  1% withdrew	Open label; blinded outcome assessment
13.3* 12.3 (P = 0.97)	<u>CVD events</u> 29.8* 27.7 (P = 0.98)	NR	<u>Taking drug at end</u> 77% 93%  <1% withdrew	Open label; blinded outcome assessment

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

Study (quality)	Study Age y	N groups	Blood pressure control	MI
INSIGHT 2000 <sup>69</sup> (Diabetes subgroup) (fair)	<u>4</u> 65	Nifedipine: 649 (GITS) Co-amiloizide: 653 (diuretic)	138/82 138/82	NR
LEWIS et al. 2001 <sup>71</sup> (Diabetics) (good)	<u>2.6</u> 58-59	Irbesartan: 579 Amlodipine: 567 Placebo: 569	140/77 141/77 144/80	NR
ABCD 2002 <sup>62</sup> (normotensive) (Diabetics) (fair)	<u>5.3</u> 58-59	Nisoldipine: 234 Enalapril: 246	132.1/78.0 132.4/78.0	7.7% 6.5% ( <i>P</i> = 0.61)
LIFE 2002 <sup>75</sup> ; LIFE 2002 <sup>74</sup> (Diabetes subgroup) (good)	<u>4.7</u> 67	Losartan: 586 Atenolol: 609	146/79 148/79	7% 8% ( <i>P</i> = 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; CAPP, Captopril Prevention Project; CVD, cardiovascular disease; D/β, 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	<u>CVD events</u> 8.3%  8.4% (NS)	NR	<u>D/C study drug</u> 33.1%  39.9%  2.4% withdrew	Double-blind; blinded outcome assessment  Randomization imbalance in diabetic subgroup
NR	<u>CV outcome<sup>†</sup></u> 23.8% 22.6% 25.3% (NS)	<u>Renal outcome<sup>§</sup></u> 32.6% ( <i>P</i> = 0.006) 41.1% 39.0% ( <i>P</i> = 0.02)	<1% withdrew	Double-blind; blinded outcome assessment  Randomized by central office
4.7% 2.4% ( <i>P</i> = 0.18)	<u>All cause mortality</u> 8.1% 7.7% ( <i>P</i> = 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% ( <i>P</i> = 0.20)	<u>All cause mortality</u> 11% 17% ( <i>P</i> = 0.002)	NR	<u>Taking drug at end</u> 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 <sup>72</sup> (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 <sup>73</sup> (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 <sup>65</sup> (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/B, 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				comments
calcium antagonists vs		ACE inhibitors vs	calcium antagonists vs	
	<u>D/B</u>	<u>D/B</u>	<u>ACEI</u>	Heterogeneity in trials comparing CA and ACEI
<u>CHD</u>	1.12*(1.00 - 1.26)	No difference for any outcome	1.23*(1.03 - 1.47)	
<u>Stroke</u>	0.87 (0.77 - 0.98)		0.98 (0.83 - 1.18)	
<u>CHF</u>	1.12 (0.95 - 1.33)		1.22 (1.00 - 1.49)	
<u>CVD events</u>	1.02 (0.95 - 1.10)		1.09 (0.99 - 1.20)	
<u>Mortality</u>	1.01 (0.92 - 1.11)		0.97 (0.85 - 1.10)	
<u>All other drugs, all participants</u>		<u>CA, all participants</u>	<u>All other drugs, diabetics</u>	Diabetics qualitatively same as all participants, but with higher ORs
<u>MI</u>	1.26† (1.11 - 1.43)	1.43† (1.15 - 1.76)	1.53† (1.01 - 2.31)	
<u>Stroke</u>	0.90 (0.80 - 1.02)	1.01 (0.84 - 1.23)	1.37 (0.86 - 2.20)	
<u>CHF</u>	1.25 (1.07 - 1.46)	1.24 (1.00 - 1.55)	1.76 (0.97 - 3.21)	
<u>CVD events</u>	1.10 (1.02 - 1.18)	1.18 (1.04 - 1.33)	1.44 (1.09 - 1.91)	
<u>Mortality</u>	1.03 (0.94 - 1.13)	0.97 (0.83 - 1.13)	1.24 (0.84 - 1.83)	
		<u>D/B or CA</u>		Heterogeneity when UKPDS added in; results are for other 3 trials without UKPDS
NA	<u>MI</u>	0.37‡ (0.24 - 0.57)	NA	
	<u>Stroke</u>	0.76 (0.48 - 1.22)		
	<u>CVD events</u>	0.49 (0.36 - 0.67)		
	<u>Mortality</u>	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.<sup>89-101</sup> Aspirin also effectively reduces CHD events in both diabetic persons and nondiabetic persons with a similar relative risk reduction (about 30%).<sup>102-106</sup>

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.<sup>107</sup> 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).<sup>99</sup> 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.<sup>108</sup> 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,<sup>109-111</sup> 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,<sup>112</sup> 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.<sup>12</sup> 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.<sup>34-39,85,113-115</sup> 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.<sup>12,41</sup>

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.<sup>116-120</sup> 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.<sup>117,119,120</sup> 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.<sup>121</sup>

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.<sup>122</sup> 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.<sup>123-128</sup> 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.<sup>129,130</sup>

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.<sup>10</sup> The most common side effect of ACE inhibitors, a reversible cough, occurs in 5% to 20% of patients and is dose-related.<sup>131</sup> 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.<sup>132,133</sup>

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.<sup>134-136</sup> 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	Add'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;<sup>10</sup>
- b) Relative risk reduction for blindness with tight glycemic control is same as relative risk reduction for photocoagulation.<sup>10</sup>

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)<sup>10</sup> 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.<sup>137</sup> Many of these groups also have a higher incidence and prevalence of such diabetic complications as ESRD and higher overall mortality rates.<sup>138</sup> 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 <sup>†</sup>		
Screening 1,000 hypertensives <sup>‡</sup> 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)

<sup>†</sup>Assumptions:

- a) 7.5% 5-year risk of CVD event with usual blood pressure control;<sup>60</sup>
  - b) 50% relative risk reduction in CVD events with tight blood pressure control.<sup>59</sup> 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.
- <sup>‡</sup>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)<sup>139</sup> 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.

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139. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering

# Appendix

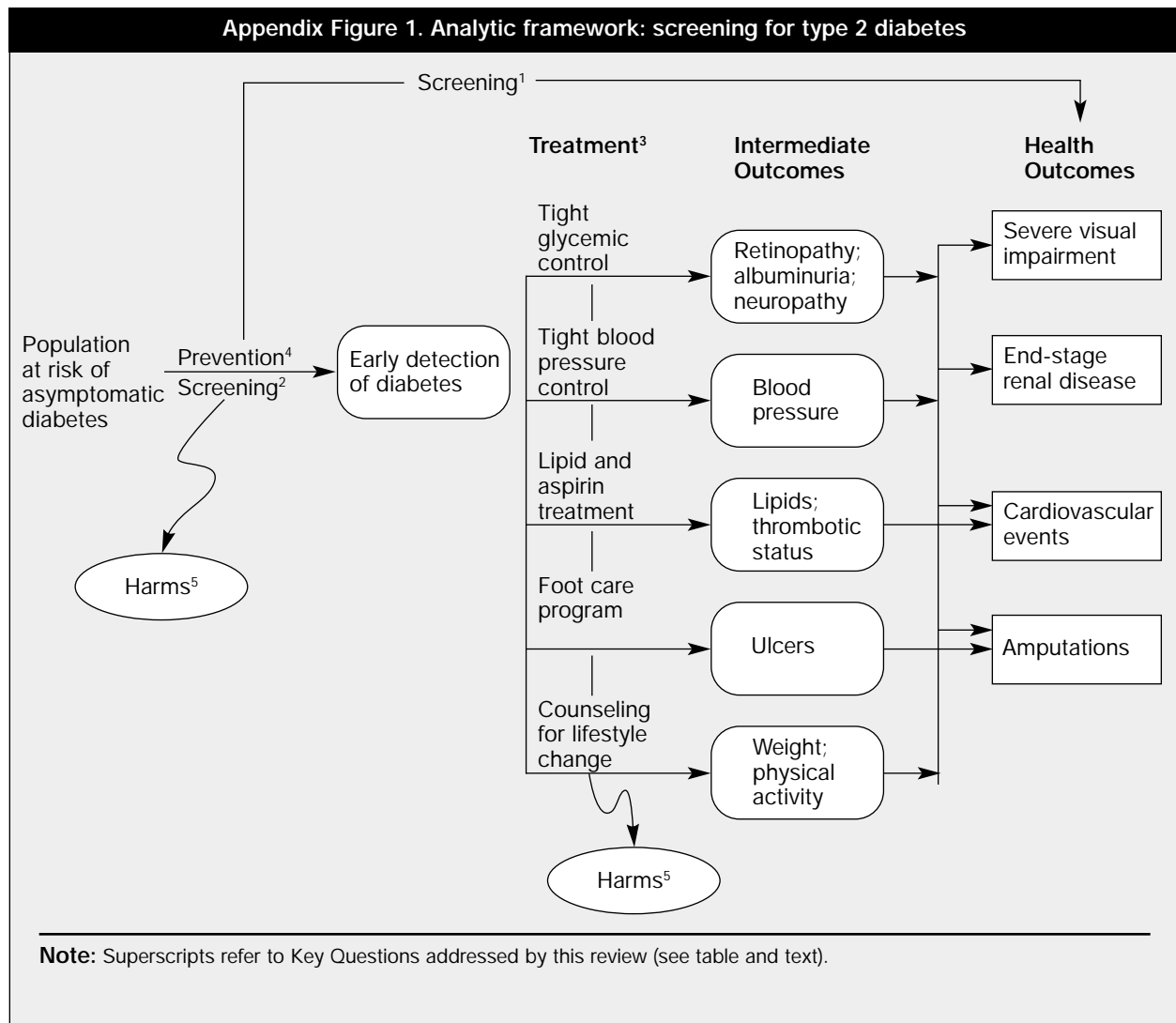
## Methods

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



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
<b>All</b>	<b>Published 1/1/94–7/30/02</b> <b>English Language</b> <b>MEDLINE, Cochrane</b> <b>Human subjects</b>		
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 $\geq 2$ years	426	13
Lipid and aspirin treatment	$\geq 75\%$ 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 unscreened (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 Mellitus,” on the AHRQ Web site at [[www.preventiveservices.ahrq.gov](http://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.

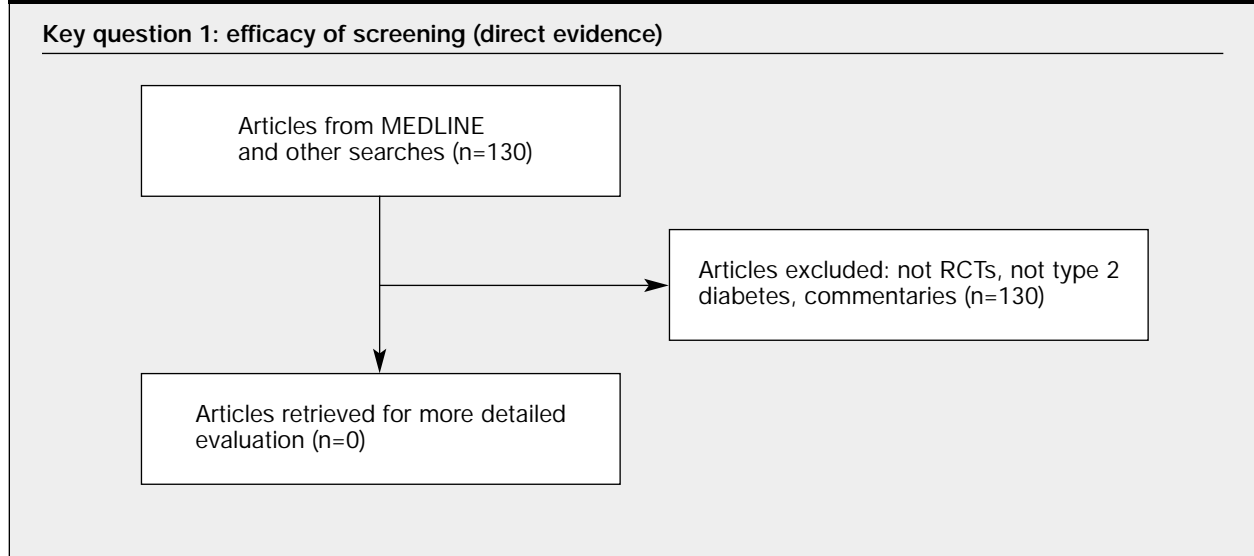


Appendix Table 2. Search strategies

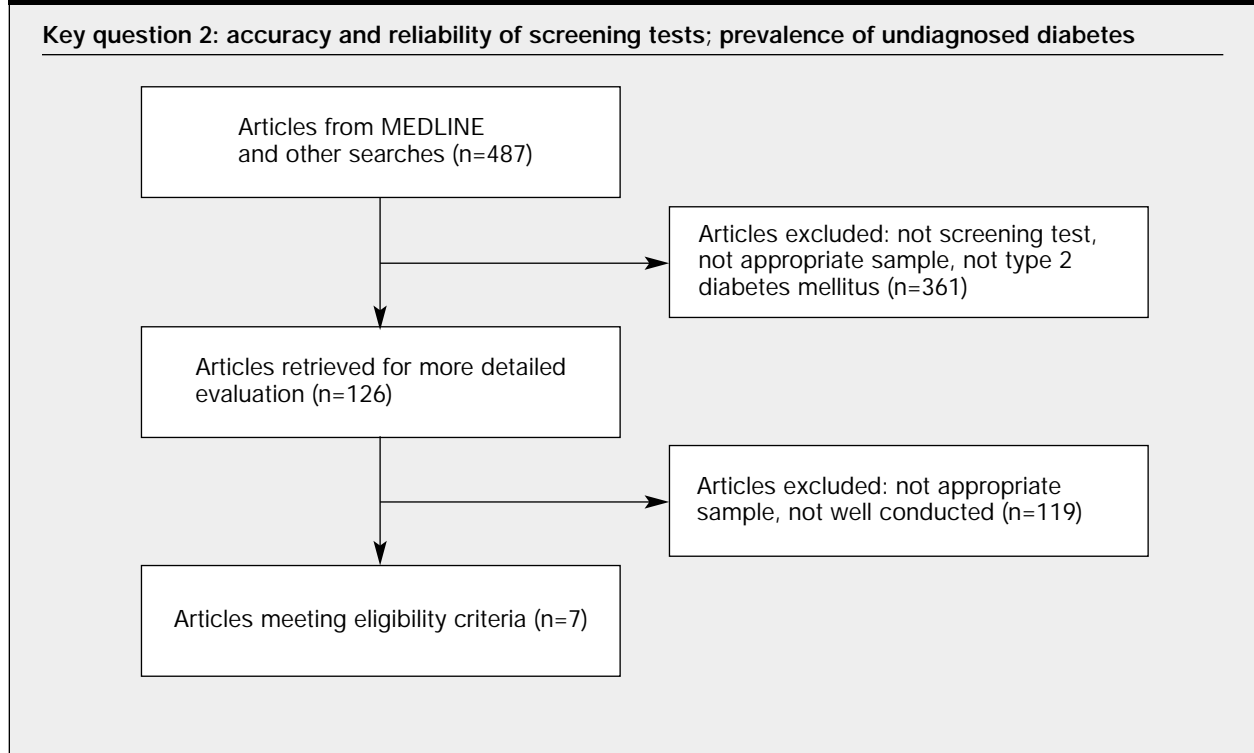
Key question	Search strategy
1: Is there direct evidence from a randomized controlled trial (RCT) of screening that screening for diabetes improves health outcomes?	NIDDM Mass screening RCT
2: What is the yield of screening?	NIDDM Prevalence, incidence Fasting glucose Random glucose Post-load glucose Glucose tolerance test Mass screening Hemoglobin A1C 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? <ul style="list-style-type: none"> <li>• tight glycemic control</li> <li>• tight blood pressure control</li> <li>• lipid and aspirin treatment</li> <li>• foot care programs</li> <li>• counseling for lifestyle change</li> </ul>	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

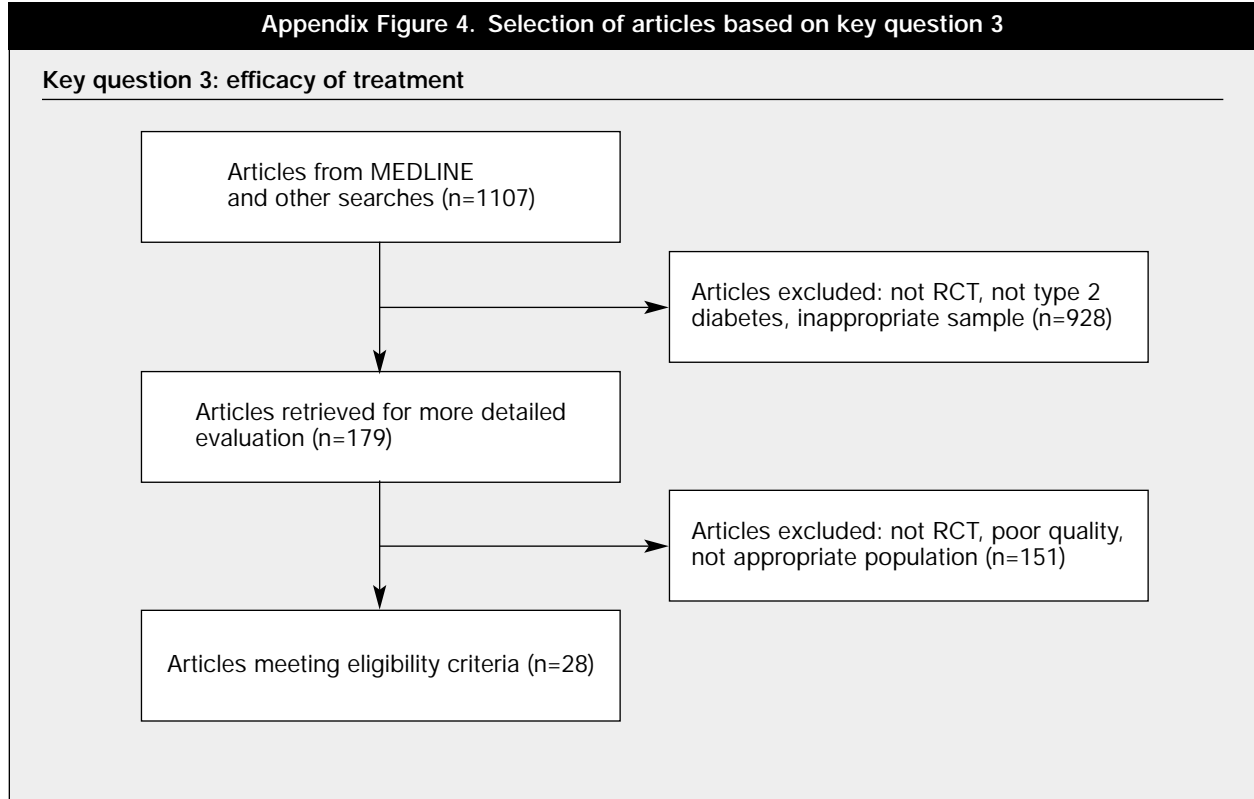
Appendix Figure 2. Selection of articles based on key question 1



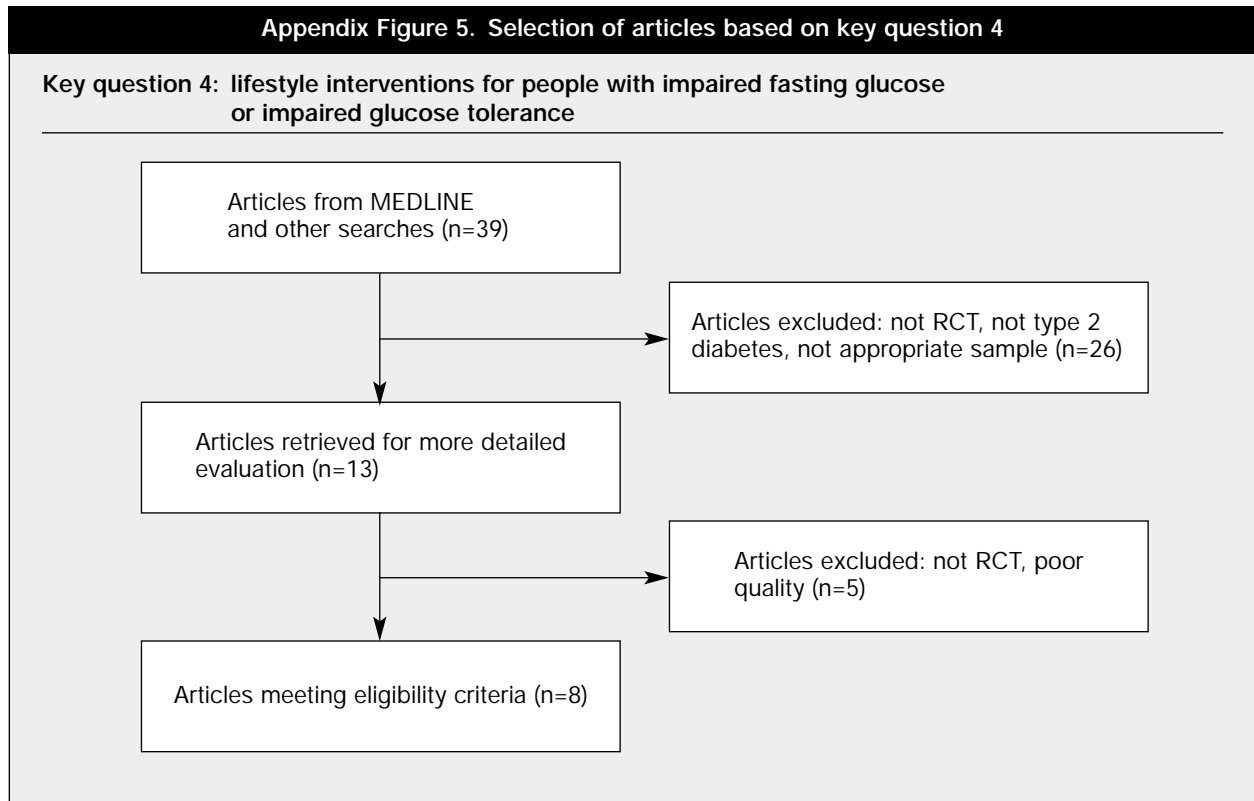
Appendix Figure 3. Selection of articles based on key question 2



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



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



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

