Screening for Type 2 Diabetes and Dysglycemia


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Type 2 diabetes mellitus (T2DM) and dysglycemia (impaired glucose tolerance and/or impaired fasting glucose) are increasingly contributing to the global burden of diseases. The authors reviewed the published literature to critically evaluate the evidence on screening for both conditions and to identify the gaps in current understanding. Acceptable, relatively simple, and accurate tools can be used to screen for both T2DM and dysglycemia. Lifestyle modification and/or medication (e.g., metformin) are cost-effective in reducing the incidence of T2DM. However, their application is not yet routine practice. It is unclear whether diabetes-prevention strategies, which influence cardiovascular risk favorably, will also prevent diabetic vascular complications. Cardioprotective therapies, which are cost-effective in preventing complications in conventionally diagnosed T2DM, can be used in screen-detected diabetes, but the magnitude of their effects is unknown. Economic modeling suggests that screening for both T2DM and dysglycemia may be cost-effective, although empirical data on tangible benefits in preventing complications or death are lacking. Screening for T2DM is psychologically unharmful, but the specific impact of attributing the label of dysglycemia remains uncertain. Addressing these gaps will inform the development of a screening policy for T2DM and dysglycemia within a holistic diabetes prevention and control framework combining secondary and high-risk primary prevention strategies.

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADDITION, Anglo Danish Dutch Study of Intensive Treatment In peOple with screen-detected diabetes in primary care; CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; UKPDS, United Kingdom Prospective Diabetes Study.

INTRODUCTION

Strong evidence exists for the effectiveness of interventions to prevent type 2 diabetes mellitus (T2DM) among people with impaired glucose tolerance (IGT) (1, 2). This evidence has led to recommendations to identify people with “dysglycemia” (i.e., IGT and/or impaired fasting glucose (IFG)) and to implement diabetes prevention interventions (3). IGT/IFG and T2DM are part of a continuum; hence, the issues concerning screening for each are inseparable. It is justifiable to talk of and evaluate screening for both conditions together. Indeed, evidence from a modeling study suggests that combining screening for T2DM with screening for IGT is more likely to be cost-effective than screening for undiagnosed diabetes alone (4). The topic of screening for T2DM has been debated for some time and various reviews have been written (5–13), although they have focused on individual aspects of screening. Gaps regarding the collective issues associated with screening across the spectrum of dysglycemia and T2DM have not been fully described, nor have the implications for primary and secondary prevention. This review aims to update and critically evaluate the evidence on screening for both T2DM and dysglycemia using the Wilson and Jungner criteria (14).

EVIDENCE ACQUISITION

We searched the Medline, ClinicalTrials.gov registry, and Cochrane databases up to April 2010 for published observational studies, randomized controlled trials, or reviews that addressed T2DM, IFG, and IGT in relation to each of Wilson and Jungner’s criteria (14) (refer to the Web Appendix and Web Table 1, both of which are posted on the Epidemiologic Reviews Web site (http://epirev.oupjournals.org/)). We did not limit by date, language of publication, or
country. We also examined the reference lists of articles identified. We used randomized controlled trials to assess the effectiveness of interventions for diabetes and dysglycemia (IFG and/or IGT). We rated identified systematic reviews addressing treatment effects or cost-effectiveness by using commonly accepted criteria (15), and we included only good-quality reviews. We relied on these reviews’ extensive assessment of the quality of the individual studies. We assessed the internal validity of individual studies that were not part of any previous systematic review and included those deemed to be of good quality (15).

The use of stringent and well-circumscribed selection criteria for including published articles may not be useful for addressing as complex and vast a question as screening for hyperglycemia, which incorporates many different questions and spans many areas. We examined papers across a broad range of pathophysiology, public health, and psychosocial literature incorporating various types of studies, which are difficult to target with a single and unifying search strategy. Thus, this review does not systematically assess every published article addressing this subject; rather, we seek to provide a synthesis of the most up-to-date, relevant, and key literature regarding screening for hyperglycemia.

EVIDENCE SYNTHESIS

The burden of hyperglycemia

T2DM. The International Diabetes Federation estimates that globally, adult diabetes prevalence among those aged 20–79 years was 6.4% (affecting 285 million people) in 2010 and will increase to 7.7% (439 million adults) by 2030 (16). Population-based estimates from the United States indicate that 40% of people with diabetes remained undiagnosed in 2006 (17). In regions of the world with less developed systems for diabetes detection and management (e.g., China), the proportion of people with undiagnosed diabetes could be 50% or higher (18).

T2DM is a major cause of premature mortality. The risk of death for people with diabetes is about twice that of persons without diabetes (19). In 2009, the estimate of excess deaths attributable to diabetes worldwide was 6.8% (3.96 million in those aged 20–79 years) (20). Mortality attributable to diabetes may currently be underestimated because diabetes is frequently omitted from death certificates; estimates do not account for deaths due to undiagnosed diabetes (20) or those deaths for which diabetes was a significant risk factor (e.g., deaths due to ischemic heart disease and stroke) (21).

T2DM causes major morbidity. In the United States, as many as 37.2% of people with diabetes aged 35 years or older also have cardiovascular disease (22), with ischemic heart disease being 2–14 times more prevalent in people with diabetes (depending on the age group) than in those without the disease (22). Diabetes is the most common risk factor for end-stage renal disease, accounting for up to 40% of cases in the United States (22). Approximately 25% of Americans with diabetes report visual impairment (23). Compared with age-matched people without diabetes, those with diabetes aged 40 years or older exhibit higher prevalence rates of peripheral arterial disease (8.0% vs. 3.9%), peripheral neuropathy (18.5% vs. 10.5%) (24), and lower-extremity diseases (arterial disease, neuropathy, foot ulcer or amputation) (26.3% vs. 15.5%) (24). Compared with normoglycemia, T2DM is also associated with a significant excess risk of a number of disabling conditions: about 2-fold for depression (25), 1.2–1.7-fold for cognitive decline (26), 1.6-fold for dementia (26), 1.7-fold for hip fracture (27), and 2–3-fold for physical disability (28, 29).

The economic burden of diabetes is also very high. Annual global health expenditures related to diabetes were projected to total at least US $376 billion (12% of all health expenditures) in 2010 and to be US $490 billion in 2030 (30). Again, these estimates would be higher if disease-related medical costs for people with undiagnosed diabetes were recognized and accounted for (e.g., in the United States, medical costs would potentially increase by US $7–$20 billion) (31, 32).

Dysglycemia. The International Diabetes Federation estimate for the global prevalence of IGT was 7.9% among adults (aged 20–79 years) in 2010 and will increase to 8.4% by 2030. Almost 30% of Americans have either IGT or IFG (17), and more than 40% of those aged 20 years or older have hyperglycemia (IGT, IFG, or T2DM) (17).

Several cohort studies have shown a gradient of increasing mortality risk from normoglycemia to IFG, to IGT, and finally to diabetes (33–39). The relative risks for mortality among men and women, respectively, are approximately 21% and 8% higher for IFG and 51% and 60% higher for IGT than for normoglycemia (33). On average, both IGT (relative risk = 1.20, 95% confidence interval (CI): 1.12, 1.28) and IGT (relative risk = 1.20, 95% CI: 1.7, 1.28) are associated with a 20% increase in cardiovascular disease risk compared with normoglycemia (40). It has also been clearly established that microvascular complications are associated with dysglycemia (24, 41–45); as many as 7.9% of people with dysglycemia had signs of retinopathy in the Diabetes Prevention Program (43); the prevalence of neuropathy is higher among people with IFG compared with those with normoglycemia (11.9% vs. 10.5%) (24); and people with IGT and/or IFG have a higher prevalence of chronic kidney disease compared with those with normoglycemia (17.7% vs. 10.6%) (45). As such, IGT and IFG, compared with normoglycemia, have also been shown to be associated with higher medical costs (46, 47).

The natural history of T2DM

The natural history of T2DM (Figure 1) includes an asymptomatic phase comprising dysglycemia and preclinical diabetes (48, 49). The pathogenesis of T2DM is not fully understood but involves gene-environment interactions, which increase susceptibility to developing 3 metabolic defects: insulin resistance, insulin secretory defect(s), and increased glucose production by the liver (48–50). The primary defects are believed to be insulin resistance and early pancreatic β-cell susceptibility (linked to predisposing genes) (51), which are worsened by several factors, including obesity and physical inactivity (50, 51). As the disease progresses, more global pancreatic defects result in
increased hepatic glucose production. Together, these defects lead to further elevations in fasting plasma glucose, a stage termed IFG by both the American Diabetes Association (52) and World Health Organization (53). If insulin resistance is severe enough, IGT is said to appear. Both IFG and IGT increase the risk of progressing to T2DM (50).

Persistent and increasing hyperglycemia further diminish the β-cells’ capacity to secrete enough insulin to compensate sufficiently for the level of insulin resistance (49–51).

Identifiable dysglycemic phase. Both IFG and IGT are asymptomatic, intermediate states of abnormal glucose regulation that precede overt T2DM (49). Persistent and increasing hyperglycemia further diminish the β-cells’ capacity to secrete enough insulin to compensate sufficiently for the level of insulin resistance (49–51).

Identifiable latent phase of diabetes. Studies of people with newly conventionally diagnosed or screen-detected T2DM provide evidence of early diabetes-related tissue damage during the preclinical phase. In the United Kingdom Prospective Diabetes Study (UKPDS), 50% of newly diagnosed diabetes cases had evidence of diabetes-related complications (57–59). In the Hoorn screening study (60, 61), the prevalences of myocardial infarction (13.3% vs. 3.4%) and ischemic heart disease (39.5% vs. 24.1%) were higher in screen-detected patients than in newly conventionally diagnosed patients, although the proportions with peripheral arterial disease were similar in both groups (10.6% vs. 10.2%). In the Anglo Danish Dutch Study of Intensive Treatment In pOple with screeN-detected diabe tes in primary care (ADDITION), screen-detected people had high estimated 10-year absolute risks of coronary disease events (11% in women and 21% in men) (62) and composite cardiovascular disease (38.6% in men and 24.6% in women) (63). With regard to microvascular sequelae of diabetes, the Hoorn study showed a higher prevalence of retinopathy in screen-detected patients than in newly conventionally diagnosed patients (7.6% vs. 1.9%), while the prevalence of impaired foot sensitivity was similar in both groups (48.1% vs. 48.3%) (64). In US population-based surveys, compared with people without diabetes, those with undiagnosed diabetes had a significantly higher

Figure 1. Steps in the natural history of type 2 diabetes mellitus.
prevalence of chronic kidney disease (41.7% vs. 10.6%) (45) and neuropathy (11.6% vs. 10.5%) (24).

**Screening tests or tools**

Previous reviews (6, 7) have reported on the advantages and limitations of a number of screening tests and tools. These have included questionnaires/risk scoring tools and the following biochemical tests: urine glucose, serum fructosamine, random blood glucose, fasting plasma glucose and glycated hemoglobin (HbA1c), and the 75-g oral glucose tolerance test (OGTT). Here, we focus on recent developments concerning these instruments and present those not known to have been previously evaluated.

**Questionnaires/risk scores.** Various instruments have been developed to identify people at high risk of having or developing T2DM or dysglycemia. These tools are based on risk factors that would help identify the minority of the population that accounts for the majority of people with T2DM and dysglycemia (65). The risk appraisal tools are presented in Web Table 2 (http://epirev.oupjournals.org/), and they involve use of self-reported questionnaires (66–71); health service data (72–74); or collected anthropometric, lifestyle, or biochemical data (68–70, 75–94). Questionnaires, whose performance depends on the response rate, may create undue anxiety or false reassurance, but they are likely to be more acceptable, less costly, and less time-consuming to administer than blood glucose testing or anthropometric measurements for risk prediction. Use of existing health service data can limit the proportion of those who need to undergo blood glucose measurements to 20%–25% of the entire population, but this tool may be limited by the availability of data on key variables. In general, including at least one blood glucose measurement improves the performance of a risk tool. However, adding complex indices of glucose or insulin metabolism to simple clinical measurements does not seem to further improve the prediction of T2DM (85, 89). Similarly, adding genetic information to common phenotypic risk factor data does not improve risk prediction in adults (95–103).

Scoring systems were first developed in Caucasian populations. Some have now been developed and/or validated for multiethnic populations (70–75, 78, 79, 83, 89–91, 104–106) and others for entirely non-Caucasian populations (76, 77, 81, 82, 84, 87, 107–109).

If the risk tools (66, 67, 69, 72, 74, 79, 81, 82, 87, 88, 90) developed and validated on the basis of prevalence studies were used as part of a repeated screening program (identification of prevalent cases at baseline and only incident cases in subsequent rounds), performance of the tools would likely change. However, at least one tool (72) developed using cross-sectional data was retested in a prospective design and showed no major change in predictive ability (110). The most widely validated and used risk assessment tool is the Finnish risk score (68). It uses weighted data for 8 risk characteristics to calculate an overall score that predicts 10-year absolute risk of T2DM.

In summary, the existing simple tools to identify high-risk people are pragmatic. However, compared with OGTT, none of these tools is optimal. The efficiency of the tools may vary over time within a population (changing prevalence of risk factors), between populations and geographic areas, and they typically perform well in populations in which they were developed (111, 112).

**Biochemical tests.** Table 2 summarizes the practical advantages and limitations of the biochemical tests that have been evaluated for T2DM screening.

**Table 1. Diagnostic Criteria for Impaired Fasting Glucose and Impaired Glucose Tolerance**

<table>
<thead>
<tr>
<th>Test</th>
<th>American Diabetes Association Criteria</th>
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<tr>
<td></td>
<td>World Health Organization Criteria</td>
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<tr>
<td>Fasting plasma glucose</td>
<td>≤5.6 mmol/L and ≤7.0 mmol/L if measured</td>
</tr>
<tr>
<td>2-hour plasma glucose after ingestion of a 75-g glucose load</td>
<td>≥7.8 mmol/L and ≤11.1 mmol/L if measured</td>
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**Urine glucose.** The sensitivity of urine glucose testing is low (16%–64%), and the positive predictive value ranges from 11% to 37% (6). Thus, glycosuria appears to be a poor screening instrument for diabetes; large proportions of individuals with diabetes would be misclassified and remain undetected.

**Random blood glucose.** The use of random blood glucose as a screening tool is somewhat limited by its low screening performance (7). A large study comparing random blood glucose with OGTT for screening recommended a cost-effective random blood glucose cutoff of ≥6.9 mmol/L. At this level, random blood glucose exhibited 93% specificity and 41% sensitivity. In terms of identifying dysglycemia, the specificity was still high, at 94%, but sensitivity was only 23% (113). A recent expert panel recommended a random blood glucose cutoff of ≥7.2 mmol/L, which has a sensitivity of 63% and specificity of 87%, based on validation against OGTT (114).

**Fasting plasma glucose.** The fasting plasma glucose screening test for hyperglycemia may have modest sensitivity (7). A Korean study found that a fasting plasma glucose threshold of ≥7 mmol/L detected only 55.7% of people with diabetes based on diagnosis by OGTT, with 100% specificity (115). An optimal cutoff for fasting plasma glucose was 100% mmol/L with a sensitivity of 85.2%, but specificity was decreased to 88.5%. A study of young African American patients with dysglycemia found fasting plasma glucose not sensitive for the diagnosis of IGT compared with OGTT (116). A fasting plasma glucose threshold of ≥5.6 mmol/L detected only
<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Urinary glucose</td>
<td>Does not require a blood sample; can be tested in fasting, random, or postprandial state; rapid processing time; inexpensive</td>
<td>Inability to measure glucose above the renal threshold; variable renal threshold; affected by fluid intake and urine concentration; not fully quantitative</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>Easy to obtain; no fasting required; inexpensive</td>
<td>Requires prompt processing (&lt;2 hours), thus the potential for error; point measurement can be affected by several factors (short-term lifestyle changes, time since prior meal, etc.)</td>
<td>Can be used</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>Relatively inexpensive and simple; single plasma glucose level measured; highly correlated with presence of complications</td>
<td>Requires the patient to fast overnight (at least 8 hours), potential for processing error; point measurement can be affected by short-term lifestyle changes; risks of phlebotomy</td>
<td>Can be used</td>
</tr>
<tr>
<td>75-g oral glucose tolerance test</td>
<td>Current “gold standard” for diagnosis of diabetes; most sensitive test for impaired glucose tolerance</td>
<td>Requires 8-hour fast, lengthy, and requires commitment of nursing staff; overall test-retest reproducibility lower than with other tests</td>
<td>Can be used</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Stable marker of long-term glycemic level; no fasting required, can be completed at any time; not affected by short-term lifestyle changes; requires only venous blood or a point-of-care testing capillary sample; lower intraindividual variability (&lt;2%) than fasting plasma glucose</td>
<td>Value may vary with assay method used; possible nonglycemic causes of error such as hemoglobinopathies and anemia; may be insensitive for detection of impaired fasting glucose or impaired glucose tolerance; high cost (more expensive than glucose testing); limited availability in some areas of the world</td>
<td>Can be used</td>
</tr>
<tr>
<td>50-g glucose challenge test</td>
<td>No fasting required; not influenced by time of day</td>
<td>Cumbersome to administer; test-retest reproducibility unclear</td>
<td>Can be used</td>
</tr>
<tr>
<td>Capillary blood glucose measurement (point-of-care testing)</td>
<td>Simple; inexpensive; no phlebotomy required</td>
<td>Imprecision may be high; not standardized</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>Marker of glycemic level over several weeks; may be an alternative to HbA1c in case of hemoglobinopathy</td>
<td>Can be influenced by serum protein or albumin levels, no clear association between the concentration and chronic complications of diabetes; performance may be limited</td>
<td>Not recommended</td>
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Abbreviation: HbA1c, glycated hemoglobin.
28.9% of IGT cases, whereas OGTT identified 87.4% of cases.

Glycated hemoglobin. Although wider consensus is still forthcoming, the American Diabetes Association recently adopted HbA1c as a diagnostic test for diabetes at a threshold of ≥6.5% (117). This adoption was justified by the alignment of the associations between HbA1c and fasting plasma glucose with diabetes complications (particularly retinopathy) and the stronger correlation of HbA1c with risks of cardiovascular disease and all-cause mortality compared with fasting plasma glucose (118). However, the new American Diabetes Association criteria using HbA1c do not specifically define IFG and IGT categories but rather a “high-risk” category corresponding to an HbA1c between 5.7% and 6.4%.

The performance of HbA1c ≥6.5% for T2DM diagnosis is variable in studies. There are suggestions of reasonable agreement with American Diabetes Association/fasting plasma glucose diagnostic criteria (coefficient of agreement κ = 0.60) (119) but lower agreement with OGTT diagnostic criteria (κ = 0.12, about 85% of people with HbA1c ≥6.5% classified as non-T2DM, and a sensitivity/specificity of 44%/79%) (120). Comparisons of HbA1c ≥6.5% with World Health Organization and American Diabetes Association criteria within the same study showed that it identifies only one-third of people diagnosed with T2DM by World Health Organization criteria (fasting plasma glucose and/or OGTT) and 70% of those detected by American Diabetes Association criteria (fasting plasma glucose alone) (121). The effect of HbA1c ≥6.5% on T2DM prevalence compared with glucose criteria may be ethnicity dependent—lower in the United States in comparison to fasting plasma glucose and/or OGTT (122) and lower in English, Australian, Greenland and Kenyan populations in comparison to OGTT (123) but higher in Danish and Indian populations in comparison to OGTT (123).

In terms of HbA1c as a screening tool for undiagnosed diabetes, a review of 63 studies indicated that an HbA1c between 5.8% and 6.3% corresponded with 66.5%–70.5% specificity and 97%–98% sensitivity (124), whereas 6.1%–6.2% was optimal in terms of sensitivity (124). HbA1c ≥6.1% would have a 63.2% sensitivity and 97.4% specificity for screening for T2DM (125); this value corresponds most closely with a 2-hour postprandial glucose concentration of 11.1 mmol/L and included 41% of nondiabetic subjects and 21% of subjects with IGT (126). The HbA1c test may not separate individuals with normoglycemia from those with previously undiagnosed diabetes well; about 60% of individuals with undiagnosed diabetes detected by fasting plasma glucose may have a normal HbA1c (127).

To detect IFG/IGT, HbA1c ≥6.1% generally has a sensitivity of 50% at most for the detection of IGT (124). In a Dutch population, HbA1c ≥5.8% detected only about 30% of people with dysglycemia (128). In a Chinese population, HbA1c ≥5.7% had a sensitivity of 59.4% and a specificity of 73.9% for the detection of dysglycemia (129). In Indian Asians (130), HbA1c ≥5.6 % was optimal for IGT/IFG detection, with an area under the receiver operating characteristic curve of 0.708 for IGT, 0.632 for IFG (World Health Organization criteria), and 0.708 for IFG (American Diabetes Association criteria). In a Chinese population, the area under the receiver operating characteristic curve of HbA1c ≥5.6 % for detection of IGT/IFG was rather low: 0.47 for men and 0.51 for women (131).

In combination with either random blood glucose or fasting plasma glucose, HbA1c may add value in identifying the subgroups of individuals who need to undergo an OGTT (7, 115, 124, 132).

An effective international standardization of HbA1c is well under way (133–135). However, the costs and lack of availability of the test in low-resource settings remain legitimate concerns (114).

The 50-g oral glucose challenge test. An evaluation of the 50-g oral glucose challenge test as a screening tool for nonpregnant adults (136) found areas under the receiver operating characteristic curves of 0.90, 0.82, and 0.79 for detection of undiagnosed diabetes, undiagnosed diabetes or dysglycemia, and dysglycemia, respectively, by plasma glucose challenge test (136). This performance was unaffected by time of day or proximity to meal times and is superior to that of capillary glucose challenge test, plasma random blood glucose, capillary random blood glucose, and HbA1c. However, this study was limited by self-selection of participants (only black and white racial groups were included), lack of measures of intraparticipant variability, and validation in separate populations.

Capillary blood testing: finger-prick point-of-care testing. The utility of capillary blood testing for diabetes screening is unclear. An Australian study found that point-of-care capillary glucose testing underestimated blood glucose values compared with fasting plasma glucose. The areas under the receiver operating characteristic curves for prediction of dysglycemia and diabetes were 0.76 and 0.71 for point-of-care and 0.87 and 0.81 for fasting plasma glucose, respectively (137). However, among Asian Indians (138), capillary random blood glucose cutoffs >6.0 mmol/L have reasonably good sensitivity (66.5%–70.5%) and specificity (65.5%–69.5%) for T2DM, IGT, and IFG screening.

Therapies for screen-detected patients

Therapies for undiagnosed diabetes. To our knowledge, only one published study, for which only interim results are available, has directly explored the benefit of early treatment in an exclusively screen-detected diabetes cohort (139). Given the paucity of direct evidence, data from intervention studies comparing the effects of treatment with lower blood glucose, blood pressure, and serum cholesterol in conventionally diagnosed diabetic populations can be examined to investigate the benefits of an early treatment for T2DM.

Glycemic control. Although the individual randomized controlled trials of aggressively targeting near-normal levels of HbA1c versus achieving less stringent glycemic control showed no significant benefits in reducing cardiovascular disease outcomes, 3 meta-analyses (140–142) combined the data and suggested at least some incremental benefits of tight glycemic control on cardiovascular disease events (mainly driven by a reduction in coronary heart disease events) but not on cardiovascular deaths or all-cause
mortality. These meta-analyses combined different permutations of estimates from the UKPDS (UKPDS 33 (143) and 34 (144)), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (145), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (146), Veterans Affairs Diabetes Trial (147), and PROactive (148, 149) trials.

Ray et al. (140) found a 17% (95% CI: 7.25) relative risk reduction in nonfatal myocardial infarction and a 15% (95% CI: 7.23) relative risk reduction in coronary heart disease events, but no reduction in stroke (odds ratio = 0.93, 95% CI: 0.81, 1.06). Kelly et al. (142) did not include the PROactive study (not designed to assess tight vs. less tight glycemic control) and found a 10% (95% CI: 2.17) relative risk reduction in cardiovascular disease events. These 2 meta-analyses are limited by the erroneous double counting of events in the overlapping control populations of the UKPDS 33 (143) and 34 (144) publications. Turnbull et al. (141) did not include PROactive and UKPDS 34; they found a 9% (95% CI: 1.16) relative risk reduction in major cardiovascular disease endpoints primarily because of a 15% (95% CI: 6.24) reduction in myocardial infarction.

The UKPDS is the only study involving newly diagnosed T2DM patients, thereby providing the closest obtainable estimates of the likely effect of glycemic control during the lead time. The 10-year posttrial monitoring results showed that tight glycemic control reduced myocardial infarction by 15% (P = 0.01) and 33% (P = 0.005) in the sulfonylurea-insulin and metformin groups, respectively (150), compared with the control group.

Lipid-lowering therapy. A meta-analysis of 12 trials (statins and fibric acid derivatives studies) reported that lipid-lowering therapy is equally efficacious in people with and without diabetes for primary and secondary prevention of cardiovascular disease (151). In primary prevention, the use of lipid-lowering drugs was associated with a 21% (95% CI: 11.30) relative risk reduction in major coronary events in patients with diabetes. The corresponding risk reduction for those with previous cardiovascular disease was also 21% (95% CI: 10.31). The absolute risk difference, however, was 3 times higher for secondary prevention (151). In addition, except for the Collaborative Atorvastatin Diabetes Study (152), these trials were not specifically aimed at people with diabetes and demonstrated these results in only post-hoc analyses of subpopulations with diabetes. The Collaborative Atorvastatin Diabetes Study (152), a primary prevention trial conducted exclusively among patients with T2DM, showed a 37% (95% CI: 17.52) relative reduction in cardiovascular events. This reduction was independent of baseline level of cholesterol. Similar findings were reported in the Heart Protection Study (153) demonstrating a 22% (95% CI: 13.30) relative reduction in cardiovascular events in the subpopulation with diabetes. Regarding the combined use of statins and fibrates, the ACCORD lipid trial showed no incremental benefit over use of statins alone in high cardiovascular disease–risk T2DM patients (154).

Antihypertensive treatment. In the UKPDS, tight blood pressure control compared with less tight control significantly reduced macrovascular and microvascular risks for patients with newly diagnosed diabetes (155). A meta-analysis of trials showed that major cardiovascular events were reduced to a comparable extent (relative risk = 0.64, 95% CI: 0.46, 0.89) in individuals with and without diabetes by regimens based on angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin II receptor blockers, diuretics, and β-blockers; the differential effect of drug classes on cardiovascular disease mortality was less clear (156).

Use of angiotensin II receptor blockers provided greater protection against congestive heart failure for those with diabetes than for those without diabetes. Use of angiotensin-converting enzyme inhibitors (e.g., ramipril) may have beneficial effects over and above blood pressure lowering, with a 25% (95% CI: 12.36) reduction in cardiovascular events (157). In the ACCORD blood pressure trial, intensive blood pressure control (target systolic blood pressure <120 mm Hg) was not better than more moderate standards (<140 mm Hg) (158). However, ACCORD participants were people with advanced diabetes, not screen-detected disease.

Aspirin therapy. Aspirin has been shown unequivocally to be effective for secondary prevention of cardiovascular disease in people with diabetes. A meta-analysis confirmed that aspirin allocation yielded greater absolute reductions in serious vascular events (6.7% vs. 8.2% per year, P < 0.0001), total stroke (2.08% vs. 2.54% per year, P = 0.002), and coronary events (4.3% vs. 5.3% per year, P < 0.0001) (159).

Regarding primary prevention of cardiovascular disease in individuals with diabetes, the Antithrombotic Trialists’ Collaborative meta-analysis did not find a beneficial effect of aspirin on cardiovascular disease events (hazard ratio (HR) = 0.88, 95% CI: 0.67, 1.15) (159). Two other meta-analyses also reported no effect of aspirin on major cardiovascular disease events (relative risks were 0.90 (95% CI: 0.80, 1.00) (160) and 0.92 (95% CI: 0.83, 1.02) (161), respectively). The vast majority of studies included in these 3 meta-analyses were not focused on T2DM patients. The only trial (162) investigating a population entirely composed of people with diabetes reported a large reduction (HR = 0.10, 95% CI: 0.01, 0.79) in the combined endpoint of fatal coronary and cerebrovascular events, but not in the combined endpoint of fatal or nonfatal ischemic heart disease, stroke, and peripheral arterial disease (HR = 0.80, 95% CI: 0.58, 1.10) or in all-cause mortality (HR = 0.90, 95% CI: 0.57, 1.14). However, this study might have been underpowered for demonstrating a significant effect of aspirin given the low event rate observed.

Lifestyle modification. The independent effect of intensive lifestyle modification on cardiovascular disease events in people with T2DM is unknown. Intensive lifestyle modification is currently being compared with standard diabetes support and education in a trial (163), where interim 1-year results show a significant reduction in weight and improvements in fitness and cardiovascular disease risk factors: HbA1c, systolic and diastolic blood pressures, triglycerides, high density lipoprotein cholesterol, and urine albumin-to-creatinine ratio. At 4 years (164), the significant improvements in weight loss (−6.15% vs. −0.88%; P < 0.001), fitness (12.74% vs. 1.96%; P < 0.001), HbA1c (−0.36% vs. −0.09%; P < 0.001), systolic (−5.33 mm Hg vs. −2.97 mm Hg; P < 0.001) and diastolic (−2.92 mm Hg
Lifestyle interventions. The effects of lifestyle interventions on hard cardiovascular disease outcomes are still awaited. 

Multifactorial intervention: effect of combined therapies. The Steno-2 trial demonstrated the superiority of an intensified, multifactorial intervention (lifestyle modification and multidrug therapy) over conventional treatment for cardiovascular disease risk factors in patients with T2DM and microalbuminuria (165). At 7.8 years of follow-up (165), risk reductions were evident for cardiovascular disease events (HR = 0.47, 95% CI: 0.24, 0.73), nephropathy (HR = 0.39, 95% CI: 0.17, 0.87), retinopathy (HR = 0.42, 95% CI: 0.21, 0.86), and autonomic neuropathy (HR = 0.37, 95% CI: 0.18, 0.79). After 13.3 years (166), all-cause mortality (HR = 0.54, 95% CI: 0.32, 0.89), deaths from cardiovascular disease (HR = 0.43, 95% CI: 0.19, 0.94), cardiovascular events (HR = 0.41, 95% CI: 0.25, 0.67), and frequency of retinal photocoagulation (relative risk = 0.45, 95% CI: 0.23, 0.86) were all reduced. These results demonstrate the significance of early initiation of comprehensive preventive care and strategies to control risk factors. Since the Steno-2 trial involved a population with long-standing T2DM and microalbuminuria, it is unclear whether these results can be extrapolated to screen-detected patients.

Comparison of an intervention similar to the Steno-2 regimen with standard therapy for diabetes in screen-detected patients is the object of the ongoing ADDITION trial (167). Interim 1-year results of ADDITION-Netherlands showed an improvement in cardiovascular disease risk factors in intensively treated, screen-detected patients compared with those routinely treated (139). These improvements included significant changes in body mass index, systolic and diastolic blood pressures, HbA1c, and total and low density lipoprotein cholesterol. The data on incident cardiovascular disease and mortality from this trial are not yet available.

To summarize, existing therapies could be used to treat hyperglycemia and other cardiovascular disease risk factors in people with screen-detected diabetes. The individual and collective cardioprotective and renoprotective effects of these therapies have been documented in randomized trials, but only in clinically recognized patient populations, often with advanced disease. The magnitude of benefit from applying these interventions in earlier stages of T2DM is currently uncertain but may become evident from the ongoing ADDITION trial (167).

Therapies for dysglycemia. Lifestyle interventions. The efficacy of lifestyle intervention in reducing the progression from IGT to diabetes has been demonstrated in several randomized controlled trials (168–172). These trials are summarized in Table 3.

Lifestyle interventions (dietary and physical activity recommendations to achieve weight loss) have been efficacious across a broad range of ethnic groups. In 3 trials, the beneficial effects of lifestyle modification in reducing T2DM incidence persisted several years after discontinuation of the active intervention. Sustained relative reductions were evident 3 years (43%, 95% CI: 24, 57) after completion of the Finnish Diabetes Prevention Study (173), 14 years (43%, 95% CI: 19, 59) later in the Chinese Da Qing study (174), and 5.7 years (34%, 95% CI: 24, 42) after termination of the US Diabetes Prevention Program (175).

In addition to effects on diabetes incidence, lifestyle modification may also affect cardiovascular disease risk factors in people with dysglycemia. The Diabetes Prevention Program reported improvements in blood pressure, serum cholesterol, and serum triglycerides at 3-year (176) and 10-year (175) follow-ups. However, the Da Qing study (174), after 20 years of follow-up, showed no benefit of lifestyle modification for cardiovascular disease events (HR = 0.98, 95% CI: 0.71, 1.37), cardiovascular disease mortality (HR = 0.83, 95% CI: 0.48, 1.40), or all-cause mortality (HR = 0.96, 95% CI: 0.65, 1.41). However, this trial was not powered for these endpoints. Fourteen years after the active phase of the Da Qing study, the lifestyle intervention group exhibited a lower incidence of severe retinopathy than did the control group (HR = 0.53, 95% CI: 0.29, 0.99). Thus, lifestyle intervention for dysglycemia may have beneficial effects on microvascular complications (177).

Drug therapy. The efficacy of a number of drugs against placebo in the regression of IGT to normoglycemia has been shown in trials (Table 4) (178–186). The drugs proven to be efficacious include metformin (170, 172, 179), troglitazone (180, 183), rosiglitazone (146), acarbose (175), orlistat (178, 182), voglibose (185), and valsartan (186). Concerns about serious side effects limit the use of most drugs, especially troglitazone and rosiglitazone, for diabetes prevention. Acarbose was also shown to be associated with a relative risk reduction of 49% (95% CI: 5, 72) for cardiovascular events and 34% for incident hypertension after 3.3 years of follow-up (187).

Other drugs have been studied, but they showed no beneficial effect on diabetes incidence. These drugs include ramipril (HR = 0.91, 95% CI: 0.81, 1.03) (188) and nateglinide (HR = 1.07, 95% CI: 1.00, 1.15) (189).

In summary, there is robust evidence of benefits from managing dysglycemia using lifestyle intervention or drug therapy. The evidence is strongest for lifestyle intervention, which has a sustained effect and influences other cardiovascular disease risk factors. Translating this evidence into routine practice remains a challenge (190).

Hitherto, interventions for diabetes prevention have targeted high-risk people. Given the linear relation between glycemia and macrovascular complications and the approximately normal distribution of glycemia in some populations, additional benefits might be derived from small shifts in this distribution through a population strategy (191). Population strategies for diabetes prevention consisting of programs for physical activity and dietary changes targeting individuals, and policies targeting food pricing and the physical environment, are philosophically very appealing and may achieve large benefits. However, considering a population approach as the “sole” strategy to adopt for diabetes prevention is constrained by the lack of evidence proving its effectiveness. In fact, no community-wide experimental or quasi-experimental study has directly assessed its feasibility and effectiveness.

The available indirect evidence on implementing policies and population-wide interventions to change the
<table>
<thead>
<tr>
<th>Authors, Year of Publication (Reference No.)</th>
<th>Study Population</th>
<th>BMI of Participants at Entry, kg/m²</th>
<th>Duration of Follow-up, Years</th>
<th>Study Goals</th>
<th>Weight Reduction (kg) at 1 Year</th>
<th>Cumulative Incidence of Type 2 Diabetes Mellitus</th>
<th>Relative Reduction in Diabetes Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al., 1997 (168)</td>
<td>China IGT &gt;25 Men and women</td>
<td>130 diet, 141 exercise, 126 diet and exercise, 133 control</td>
<td>26</td>
<td>6</td>
<td>Weight loss; maintenance of a healthy diet and possibly exercise</td>
<td>NR</td>
<td>68% (15.7% per year)</td>
</tr>
<tr>
<td>Tuomilehto et al., 2001 (169)</td>
<td>Finland IGT 40–65 Men and women</td>
<td>265 intervention, 257 control</td>
<td>31</td>
<td>3.2</td>
<td>5% weight loss on low-fat, higher-fiber diet and 30 minutes of exercise per day</td>
<td>4.2</td>
<td>23% (6% per year)</td>
</tr>
<tr>
<td>Knowler et al., 2002 (170)</td>
<td>United States IGT &gt;25 Men and women</td>
<td>1,079 intervention, 1,082 control</td>
<td>34</td>
<td>2.8</td>
<td>7% weight loss and 150 minutes of exercise per week</td>
<td>7</td>
<td>28.9% at 3 years</td>
</tr>
<tr>
<td>Kosaka et al., 2005 (171)</td>
<td>Japan IGT &gt;30 Men</td>
<td>356 intervention, 102 control</td>
<td>24</td>
<td>4</td>
<td>Reduction in BMI to ≤22 kg/m² by exercising 30–40 minutes per day</td>
<td>2.5</td>
<td>9.3% (assessed by FPG &gt;7 mmol/L)</td>
</tr>
<tr>
<td>Ramachandran et al., 2006 (172)</td>
<td>India IGT 33–55 Men and women</td>
<td>133 intervention, 136 control</td>
<td>26</td>
<td>3</td>
<td>Weight maintenance by diet low in refined carbohydrates and fat and 30 minutes of exercise per day</td>
<td>0</td>
<td>55%</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NR, not reported.
Table 4. Randomized Controlled Trials of Treatment for Dysglycemia (Impaired Fasting Glucose/Impaired Glucose Tolerance) by Pharmacotherapy

<table>
<thead>
<tr>
<th>Authors, Year of Publication (Reference No.)</th>
<th>Study Population</th>
<th>No. of Participants Per Study Group</th>
<th>Medication</th>
<th>Duration of Follow-up, Years</th>
<th>Cumulative Incidence of T2DM in the Control Group</th>
<th>Relative Reduction in Diabetes Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heymsfield et al., 2000 (178)</td>
<td>Multicenter (United States and Europe)</td>
<td>IGT (n = 120), BMI 36 kg/m² ≥18</td>
<td>359 intervention, 316 placebo</td>
<td>Orlistat 120 mg 3 times daily</td>
<td>2</td>
<td>7.6%</td>
</tr>
<tr>
<td>Yang et al., 2001 (179)</td>
<td>China</td>
<td>IGT, BMI 25 kg/m² ≥25</td>
<td>88 intervention, 85 placebo</td>
<td>Metformin 250 mg 3 times daily</td>
<td>3.0</td>
<td>11.6% per year</td>
</tr>
<tr>
<td>Knowler et al., 2002 (170)</td>
<td>United States</td>
<td>IGT, BMI 34 kg/m² ≥25</td>
<td>1,073 intervention, 1,082 placebo</td>
<td>Metformin 850 mg twice daily</td>
<td>2.8</td>
<td>28.9%</td>
</tr>
<tr>
<td>Buchanan et al., 2002 (180)</td>
<td>United States</td>
<td>Former GDM, IGT, BMI 30 kg/m² ≥18</td>
<td>133 intervention, 133 placebo</td>
<td>Troglitazone 400 mg once daily</td>
<td>3.5</td>
<td>30%</td>
</tr>
<tr>
<td>Chiasson et al., 2002 (181)</td>
<td>Multicenter (Canada and Europe)</td>
<td>IGT, BMI 31 kg/m² 40–70</td>
<td>714 intervention, 715 placebo</td>
<td>Arcabose 100 mg 3 times daily</td>
<td>3.3</td>
<td>42%</td>
</tr>
<tr>
<td>Torgerson et al., 2004 (182)</td>
<td>Multicenter (United States and Europe)</td>
<td>IGT (n = 694), BMI 37 kg/m² 30–60</td>
<td>1,640 intervention, 1,637 placebo</td>
<td>Orlistat 120 mg 3 times daily</td>
<td>4</td>
<td>14.2%</td>
</tr>
<tr>
<td>Knowler et al., 2005 (183)</td>
<td>United States</td>
<td>IGT, BMI 31 kg/m² ≥25</td>
<td>585 intervention, 582 placebo</td>
<td>Troglitazone 400 mg once daily</td>
<td>0.9</td>
<td>12% per year</td>
</tr>
<tr>
<td>Gerstein et al., 2006 (184)</td>
<td>Multicenter (Canada and Europe)</td>
<td>IGT, IFG, or both; BMI 31 kg/m² ≥30</td>
<td>2,365 intervention, 2,634 placebo</td>
<td>Rosiglitazone 8 mg once daily</td>
<td>3.0</td>
<td>25%</td>
</tr>
<tr>
<td>Kawamori et al., 2009 (185)</td>
<td>Japan</td>
<td>IGT, BMI 26 kg/m² 30–70</td>
<td>897 intervention, 883 placebo</td>
<td>Voglibose 0.2 mg 3 times daily</td>
<td>&lt;1 (48 weeks)</td>
<td>9.4%</td>
</tr>
<tr>
<td>Mc Murray et al., 2010 (186)</td>
<td>Multicenter (United States and Europe)</td>
<td>IGT, BMI 30.5 kg/m² ≥55</td>
<td>4,631 intervention, 4,672 placebo</td>
<td>Valsartan 160 mg daily</td>
<td>5</td>
<td>36.8%</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported; T2DM, type 2 diabetes mellitus.
environment and promote a healthy lifestyle is inconclusive (190, 192, 193). Furthermore, a population strategy has economic implications that warrant consideration as well as trade-offs (190), especially because such a strategy may not provide needed preventive services to current generations of persons at high risk of developing diabetes in the near future. A sensible approach to diabetes prevention may therefore be one that does not view population and high-risk strategies for diabetes prevention as competing or mutually exclusive but rather complementary. For example, the Finnish national plan for diabetes prevention (194) combines 3 concurrent approaches: a population strategy aimed at promoting the health of the entire nation, an individualized strategy for those at high risk, and a strategy of early diagnosis and management for those with new-onset T2DM.

**Effectiveness of screening for hyperglycemia: potential benefits and harms**

Impact of screening on morbidity and mortality. There is a paucity of data on the effects of screening for T2DM and/or dysglycemia on morbidity and mortality. A 10-year, retrospective, matched case-control study using health service data suggested that screen-detected diabetes was associated with a 13% (95% CI: −62, 98) relative risk reduction in microvascular complications compared with routine diagnosis (195). Another study assessing loss of life-years showed that over 12 years, compared with age- and sex-matched persons (195). Another study assessing loss of life-years showed that over 12 years, compared with age- and sex-matched individuals with diabetes, 488 people with diabetes detected by glycosuria lost 1.96 years and people with conventionally diagnosed diabetes lost 3.42 years (P < 0.005) (196). Although case-control studies may be useful when screening is prevalent in the population (as is the case for cervical cancer), they correspond to a low level in the hierarchy of evidence for the benefits of screening because they are plagued by biases and confounding that limit interpretation. Furthermore, the existing studies either focused on microvascular complications (195) or conducted glycosuria screening (196), whose performance is very limited (6).

Randomized trials of screening comparing people offered and those not offered screening would probably provide the highest level of evidence on the effect of hyperglycemia screening on health outcomes. To date, no known trial of screening has been published, but the ADDITION-Cambridge study is under way (197).

Psychosocial impact of screening. In general, studies tend to suggest limited or no psychological effect of screening for newly detected people with T2DM. This includes no adverse or positive effects on participants’ perceived health status and well-being after being notified of the results (198–200), a low perceived risk of T2DM in screen-detected patients beforehand despite the presence of risk factors (200), and no significant impact on anxiety levels in screen-detected patients (200, 201). However, greater symptom (hyperglycemia-related) distress and negative moods have been reported in screen-detected patients in the first year following diagnosis than in nondiabetic subjects (202). Intensification of treatment in screen-detected patients may increase anxiety levels and lower self-efficacy over time (203). Comparisons of people with screen-detected diabetes with those without diabetes did not reveal any short-term (2 weeks) or long-term (6–12 months) adverse or positive effects on quality of life after diagnosis (198, 204, 205), suggesting that diabetes screening has little or no labeling effect.

The previously mentioned studies have focused on people with screen-detected diabetes, ignoring those who screened negative but may still be affected psychologically. In addition, these studies have mainly been observational, which makes them susceptible to misinterpretation because of biases. Park et al. (206), in a small trial assessing the short-term effects (6 weeks after screening) of invitation to screening, found greater anxiety among invited participants than those not invited but no difference in illness perception and self-rated health. In a subsequent and much larger trial, Eborall et al. (207) found no effect of screening on the anxiety level of invited participants (with or without diabetes at screening) compared with those not invited at any time, be it immediately after the test, at 3–6 months, or at 12–15 months.

Paddison et al. (208) found that negative test results at diabetes screening do not promote false reassurance, whether expressed as lower perceived risk, lower intentions for health-related behavioral change, or higher self-rated health. The ADDITION-Denmark study, in an observational analysis, showed that screening had no impact on lifestyle behaviors (smoking, alcohol consumption, dietary intake, or physical activity levels) a year after screening (209).

To our knowledge, no published study to date has examined the psychological effects of receiving a diagnosis of dysglycemia. However, after 9 months in a 24-month lifestyle intervention for T2DM prevention in a high-risk (with or without dysglycemia) German population, participation was not associated with higher levels of anxiety, depression, or overall psychological distress than in the general population (210).

Cost-effectiveness studies. In practice, adopting a screening policy for hyperglycemia would depend on the cost-effectiveness of both detection (i.e., yield in the population of interest) and therapies (for diabetes or dysglycemia).

Cost-effectiveness of diabetes treatment. The treatments for individual cardiovascular disease risk factors in patients with newly diagnosed T2DM have been shown to be cost-effective (211–215). A US study (212) estimated incremental cost-effectiveness ratios from a societal perspective at $41,384 per quality-adjusted life-year for intensive glycemic control, $1,959 per quality-adjusted life-year for intensified hypertension control, and $51,889 per quality-adjusted life-year for the reduction in serum cholesterol levels. Intensive multifactorial treatment in specialized care within the Danish Steno-2 study (216) was more cost-effective than conventional treatment for T2DM (cost-effectiveness ratio: 2,538 Euros per quality-adjusted life-year). It is expected that similar benefits (cost- and lifesaving) would be observed if patients were managed in primary care.

Cost-effectiveness of therapies for dysglycemia. Herman et al. (217) estimated cost-effectiveness ratios, from a health service perspective, of $1,100 and $31,300 per quality-adjusted life-year for the Diabetes Prevention Program lifestyle and metformin interventions, respectively, for people with dysglycemia. From a societal perspective, the interventions...
<table>
<thead>
<tr>
<th>Authors, Year of Publication (Reference No.)</th>
<th>Conditions Screened for</th>
<th>Approach to Screening</th>
<th>Country</th>
<th>Target Population</th>
<th>Screening Sites</th>
<th>Screening Tests</th>
<th>Diagnostic Tests</th>
<th>No. Contacted</th>
<th>No. Screened</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention Program, 2005 (258)</td>
<td>IGT and undiagnosed diabetes</td>
<td>Community</td>
<td>United States</td>
<td>Volunteers aged &gt;25 years with BMI &gt;24 kg/m² and no history of diabetes</td>
<td>27 clinical study centers</td>
<td>OGTT</td>
<td>OGTT</td>
<td>158,177</td>
<td>30,383</td>
<td>27 for IGT, 13 for T2DM</td>
</tr>
<tr>
<td>Tabaei et al., 2003 (80)</td>
<td>Undiagnosed diabetes</td>
<td>Community</td>
<td>United States</td>
<td>Volunteers aged &gt;20 years, not pregnant, and with no history of diabetes</td>
<td>Hospital sites, health fairs, shopping centers, work sites, community centers, and other sites</td>
<td>ADA screening questionnaire followed by capillary RBG (cutoff ≥160 mg/dL) or FPG (cutoff ≥126 mg/dL)</td>
<td>NR</td>
<td>3,506</td>
<td>3,301</td>
<td>0.5</td>
</tr>
<tr>
<td>Portfield et al., 2004 (259)</td>
<td>Undiagnosed diabetes</td>
<td>Community</td>
<td>United States</td>
<td>Volunteers aged &gt;20 years, not pregnant or within 3 months of being pregnant, not breastfeeding or within 6 weeks of breastfeeding, no hospitalizations in the last 6 months</td>
<td>Churches, community centers, senior centers, public housing developments, local businesses, and community organization headquarters</td>
<td>Capillary FPG</td>
<td>FPG or OGTT</td>
<td>3,356</td>
<td>2,699</td>
<td>1.7</td>
</tr>
<tr>
<td>Ealovega et al., 2004 (260)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic</td>
<td>United States (Michigan)</td>
<td>Nondiabetic members of a health maintenance organization aged ≥45 years</td>
<td>Health maintenance organization</td>
<td>Plasma RBG or whole blood RBG or HbA₁c or OGTT</td>
<td>OGTT</td>
<td>8,286</td>
<td>5,752</td>
<td>0.6</td>
</tr>
<tr>
<td>O’Connor et al., 2001 (261)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic</td>
<td>United States</td>
<td>High-risk patients with both dyslipidemia and hypertension with no history of diabetes and of screening</td>
<td>3 volunteer clinics of a multispecialty medical group</td>
<td>Plasma RBG (cutoff not specified)</td>
<td>FPG or OGTT</td>
<td>469</td>
<td>176</td>
<td>2.8</td>
</tr>
<tr>
<td>Christensen et al., 2004 (262)</td>
<td>Undiagnosed diabetes</td>
<td>Community (population-based stepwise)</td>
<td>Denmark</td>
<td>Nondiabetic volunteers aged 40–69 years</td>
<td>88 general practices</td>
<td>Self-administered risk chart, then RBG + HbA₁c, then FPG if RBG &gt;5 mmol/L and HbA₁c ≥6.1%</td>
<td>RBG ≥11 mmol/L and FPG &gt;6.0 mmol/L or OGTT if 5.6 ≤ FPG &lt; 6.1 mmol/L or HbA₁c ≥6.1%</td>
<td>60,926</td>
<td>11,263</td>
<td>4.4</td>
</tr>
<tr>
<td>Janssen et al., 2007 (263)</td>
<td>Undiagnosed diabetes</td>
<td>Community (population-based stepwise)</td>
<td>The Netherlands</td>
<td>Volunteers aged 50–70 years</td>
<td>79 general practices</td>
<td>Risk assessment by questionnaire, then RBG, and then FPG if RBG &gt;5.5 mmol/L</td>
<td>RBG &gt;11.1 mmol/L and FPG &gt;6.0 mmol/L or OGTT if FPG &gt;5.6 mmol/L ≤ FPG &lt; 6.1 mmol/L or HbA₁c ≥6.1%</td>
<td>56,978</td>
<td>17,883</td>
<td>3.3</td>
</tr>
<tr>
<td>Smith et al., 2003 (264)</td>
<td>Undiagnosed diabetes, IGT, IFG</td>
<td>Opportunistic, stepwise and systematic</td>
<td>Ireland</td>
<td>All patients aged &gt;40 years attending a study practice</td>
<td>41 general practices</td>
<td>Self-determined high risk by questionnaire and then plasma RBG</td>
<td>Plasma RBG &gt;11.1 mmol/L or OGTT if plasma RBG &gt;5.5 mmol/L</td>
<td>NR</td>
<td>3,821</td>
<td>2.2 for T2DM and 3.9 for IFG and/or IGT</td>
</tr>
<tr>
<td>Study</td>
<td>Diagnosis Type</td>
<td>Strategy</td>
<td>Country</td>
<td>Age Criteria</td>
<td>Sample Size</td>
<td>T2DM Prevalence</td>
<td>IGT Prevalence</td>
<td>IFG Prevalence</td>
<td></td>
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<tr>
<td>Klein Woolthuis et al., 2009 (265)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic and stepwise</td>
<td>The Netherlands</td>
<td>All patients aged 45–75 years</td>
<td>11 family practices</td>
<td>High risk (determined by using risk factors information from electronic records), then capillary FPG (repeat if FPG &gt; 6.1 mmol/L), and then venous FPG if both capillary FPG &gt; 6.1 mmol/L or at least 1 sample ≥ 7 mmol/L</td>
<td>Confirmatory venous FPG if first venous FPG ≥ 7.8 mmol/L</td>
<td>4.186</td>
<td>3.733</td>
<td>2.8 for T2DM</td>
</tr>
<tr>
<td>Franciosi et al., 2005 (266)</td>
<td>Undiagnosed diabetes and IGT</td>
<td>Opportunistic</td>
<td>Italy</td>
<td>Patients aged 55–75 years with one or more CV risk factors</td>
<td>109 general practitioners’ offices</td>
<td>Self-administered diabetes risk questionnaire and then OGTT</td>
<td>OGTT</td>
<td>1,840</td>
<td>1,377</td>
<td>15.4 for IFG, 11.1 for IGT, 11.0 for IGT and IFG, and 17.4 for T2DM</td>
</tr>
<tr>
<td>Colagiuri et al., 2004 (79)</td>
<td>Undiagnosed diabetes and IGT</td>
<td>Community</td>
<td>Australia</td>
<td>Age ≥ 25 years</td>
<td>42 urban and rural areas</td>
<td>Risk assessment and then FPG</td>
<td>OGTT</td>
<td>11,247</td>
<td>10,508</td>
<td>3.1 for T2DM, 9.1 for IGT and/or IFG</td>
</tr>
<tr>
<td>Edelman et al., 2002 (267)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic</td>
<td>United States</td>
<td>Outpatients aged 45–64 years</td>
<td>Major medical center (Durham Veterans Affairs Medical Center)</td>
<td>Initial HbA1c and then FPG if HbA1c ≥ 6.0% or FPG ≥ 7 mmol/L</td>
<td>Second FPG if initial FPG &gt; 7 mmol/L or OGTT if initial FPG 6.1–6.9 mmol/L</td>
<td>1,452</td>
<td>1,253</td>
<td>4.5</td>
</tr>
<tr>
<td>Lawrence et al., 2001 (268)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic</td>
<td>United Kingdom</td>
<td>Nondiabetic patients aged &gt;45 years</td>
<td>Single general practice</td>
<td>OGTT if RBG ≥ 6 mmol/L</td>
<td>FPG or OGTT</td>
<td>41,400</td>
<td>25,356</td>
<td>1.4</td>
</tr>
<tr>
<td>Goyder et al., 2008 (251)</td>
<td>Undiagnosed diabetes</td>
<td>Systematic</td>
<td>United Kingdom</td>
<td>Age &gt; 40 years with BMI &gt; 25 kg/m²</td>
<td>24 general practices covering deprived areas</td>
<td>Capillary RBG</td>
<td>OGTT if RBG ≥ 6 mmol/L</td>
<td>FPG or OGTT</td>
<td>41,400</td>
<td>25,356</td>
</tr>
<tr>
<td>Cognieu et al., 2006 (269)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic</td>
<td>France</td>
<td>Age &lt; 65 years and at least 2 risk factors for diabetes</td>
<td>288 general practitioners’ offices</td>
<td>FPG</td>
<td>Second FPG if initial FPG ≥ 7 mmol/L or OGTT if initial FPG 6.1–6.9 mmol/L</td>
<td>5,950</td>
<td>1,499</td>
<td>2.7 for T2DM and 22 for IFG</td>
</tr>
<tr>
<td>Oberfinger et al., 2008 (270)</td>
<td>IFG and/or IGT; diabetes</td>
<td>Opportunistic and systematic</td>
<td>Germany</td>
<td>All employees</td>
<td>Workplace (occupational health department)</td>
<td>FPG or RBG or OGTT</td>
<td>FPG or OGTT</td>
<td>13,170</td>
<td>0.79 for T2DM and 5.1 for IGT and/or IFG</td>
<td></td>
</tr>
<tr>
<td>Ko et al., 2000 (271)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic systematic</td>
<td>Hong Kong (China)</td>
<td>Having a known risk factor for diabetes</td>
<td>Major diabetes center</td>
<td>OGTT</td>
<td>OGTT</td>
<td>1,649</td>
<td>14.6 for T2DM</td>
<td></td>
</tr>
<tr>
<td>Bando et al., 2009 (272)</td>
<td>Undiagnosed diabetes, IFG/IGT</td>
<td>Opportunistic (systematic health check)</td>
<td>Japan</td>
<td>All adults aged 20–83 years attending hospital</td>
<td>Major hospital</td>
<td>OGTT</td>
<td>OGTT</td>
<td>14,674</td>
<td>22.5 for IFG/ IGT and 5.6 for T2DM</td>
<td></td>
</tr>
<tr>
<td>Buysschaert et al., 2001 (273)</td>
<td>Undiagnosed diabetes</td>
<td>Opportunistic (consecutive)</td>
<td>Belgium</td>
<td>Age &gt; 60 years, positive family medical history of diabetes mellitus, BMI ≥ 25 kg/m²</td>
<td>General practitioners’ offices (1,446 general practitioners)</td>
<td>Capillary RBG, FPG if RBG ≥ 5.5 mmol/L or OGTT if FPG between 5.5 mmol/L and 7.8 mmol/L</td>
<td>FPG ≥ 7.8 mmol/L or positive OGTT</td>
<td>10,201</td>
<td>11 for T2DM and 22 for IGT</td>
<td></td>
</tr>
<tr>
<td>Hanif et al., 2008 (274)</td>
<td>Glucose intolerance</td>
<td>Community based and stepwise</td>
<td>United Kingdom</td>
<td>Volunteers of south Asian origin aged 20–75 years</td>
<td>Temples and mosques</td>
<td>Risk stratification using a questionnaire and BMI (low, medium, high), then OGTT if medium or high risk</td>
<td>OGTT</td>
<td>435</td>
<td>205</td>
<td>20 for T2DM and 28.7 for IGT</td>
</tr>
<tr>
<td>Toscano et al., 2008 (275)</td>
<td>Undiagnosed diabetes</td>
<td>Community nationwide screening</td>
<td>Brazil</td>
<td>Age &gt; 40 years</td>
<td>5,301 municipalities countrywide</td>
<td>Capillary FPG (cutoff ≥ 5.5 mmol/L or RBG (cutoff ≥ 7.8 mmol/L) Not specified (referral of patients)</td>
<td>22,069,905</td>
<td>1.6 for T2DM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table continues
<table>
<thead>
<tr>
<th>Authors, Year of Publication (Reference No.)</th>
<th>Conditions Screened for</th>
<th>Approach to Screening</th>
<th>Country</th>
<th>Age/Population</th>
<th>Screening Sites</th>
<th>Screening Tests</th>
<th>Diagnostic Tests</th>
<th>No. Contacted</th>
<th>No. Screened</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al., 2009 (276)</td>
<td>Undiagnosed diabetes and IGT</td>
<td>Community-based (targeted) screening</td>
<td>Australia</td>
<td>Age &gt;35 years if Maori or &gt;50 years if Caucasian or 10 years younger if one or more of the following risk factors present: BMI &gt;30 kg/m², first-degree relative with T2DM, hypertension, triglycerides &gt;2.8 mmol/L, low HDL cholesterol, PCOS, or history of CVD</td>
<td>4 general practices</td>
<td>FPG</td>
<td>OGTT</td>
<td>1,251</td>
<td>1,002</td>
<td>3.3 for T2DM and 3.4 for IGT</td>
</tr>
<tr>
<td>Grant et al., 2004 (277)</td>
<td>Undiagnosed diabetes</td>
<td>Community</td>
<td>United States (Bronx, New York)</td>
<td></td>
<td>Churches, group homes, shelters, community centers, and street corners</td>
<td>HbA₁c</td>
<td>HbA₁c ≥ 7%</td>
<td>468</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Hersberger et al., 2006 (278)</td>
<td>Undiagnosed diabetes</td>
<td>Community</td>
<td>Switzerland</td>
<td>Not specified (but mean age: 69 years, SD: 14.1)</td>
<td>Pharmacies</td>
<td>Risk assessment with ADA questionnaire and then pharmacy risk questionnaire and then capillary FPG or RBG</td>
<td>FPG ≥ 6.1 mmol/L or RBG ≥ 11.1 mmol/L</td>
<td>93,258</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Rolka et al., 2001 (279)</td>
<td>Undiagnosed diabetes</td>
<td>Community</td>
<td>United States</td>
<td>Volunteers aged ≥20 years, except those with self-reported previously diagnosed T2DM, pregnancy or breastfeeding within the previous 3 months, or hospitalization within the previous 6 months</td>
<td>Health center (during routine visit) and at community health fairs</td>
<td>Risk assessment with ADA questionnaire or capillary RBG</td>
<td>OGTT</td>
<td>1,471</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Lindahl et al., 1999 (280)</td>
<td>IGT</td>
<td>Community</td>
<td>Sweden</td>
<td>Age 30–60 years</td>
<td>Health survey sites in one province (Vasterbotten Northern province)</td>
<td>OGTT</td>
<td>OGTT</td>
<td>21,057</td>
<td>1.2 in men and 1.3 in women for IFG, 5.5 in women and 3.6 in men for IGT</td>
<td></td>
</tr>
<tr>
<td>Leiter et al., 2001 (281)</td>
<td>Undiagnosed diabetes and glucose intolerance</td>
<td>Opportunistic and stepwise</td>
<td>Canada</td>
<td>Age &gt;40 years</td>
<td>4,000 physicians’ offices</td>
<td>Capillary RBG and then venous FPG if RBG &gt;5.5 mmol/L</td>
<td>FPG ≥ 7 mmol/L or OGTT if FPG 6.1–6.9 mmol/L</td>
<td>9,042</td>
<td>2.2 for T2DM and 3.5 for IGT and/or IFG</td>
<td></td>
</tr>
<tr>
<td>Greaves et al., 2004 (282)</td>
<td>Undiagnosed diabetes and IFG</td>
<td>Community-based targeted screening</td>
<td>United Kingdom</td>
<td>Age ≥40 years and BMI ≥ 27 kg/m²</td>
<td>16 general practices</td>
<td>FPG</td>
<td>Repeat FPG if initial FPG &gt;6.1 mmol/L (T2DM if both reading ≥7.0 mmol/L and IFG if 1 reading ≥7.0 mmol/L and 1 reading 6.1–6.9 mmol/L)</td>
<td>2,124</td>
<td>1,287</td>
<td>5.4 for T2DM and 9.7 for IFG</td>
</tr>
</tbody>
</table>
cost $8,800 and $29,900 per quality-adjusted life-year, respectively. Eddy et al. (218) reported that metformin would deliver only about one-third of the long-term health benefits achievable by the Diabetes Prevention Program lifestyle program. From a societal perspective, the Diabetes Prevention Program lifestyle intervention ($62,600/quality-adjusted life-year) or the use of metformin ($35,400/quality-adjusted life-year) was cost-effective compared with no program.

Various other cost-effectiveness models for T2DM prevention have demonstrated that lifestyle interventions (219–224), metformin (220, 222, 223), and acarbose (225) are all cost-effective compared with no intervention, with lifestyle showing the most optimal cost-effectiveness ratio.

Cost-effectiveness of screening for hyperglycemia. Waugh et al. (9) systematically reviewed the literature on the economics of screening for diabetes (226–233) and/or dysglycemia (234, 235). Despite the differences (assumptions about disease progression, heterogeneity in populations at risk, characteristics and performance of the screening tests, and screening strategies) between included studies, the overall conclusions from all these studies are the following: 1) screening for hyperglycemia would be cost-effective, 2) targeted screening of high-risk groups would be more cost-effective than universal screening, and 3) treatment is the key determinant of cost-effectiveness (9). Screening for IGT followed by lifestyle modification or metformin treatment was also cost-effective, with lifestyle modification having a better cost-effectiveness ratio (9).

Recently published economic models also demonstrate the cost-effectiveness of screening for T2DM and/or dysglycemia (particularly IFG) (4, 236–240). Detection and treatment for people with either IFG or IGT or both appeared to be much more cost-effective than detection and treatment limited to individuals with both IGT and IFG (238). Screening for T2DM and IGT followed by lifestyle intervention in those with IGT would be more cost-effective than screening for T2DM alone or screening for T2DM and IGT followed by metformin therapy (4). Age at initiation of screening, screening interval, and screening tests have also been modeled. A simulation of 9 screening strategies found that screening for T2DM in the US population would be most cost-effective if started at age 30–45 years and repeated every 3–5 years (240). A comparison of 5 opportunistic screening strategies (plasma or capillary random blood glucose, HbA1c, plasma or capillary glucose challenge test, and subsequent OGTT) for T2DM and dysglycemia in the United States found the glucose challenge test to be an inexpensive and cost-saving method from a health care perspective and cost-neutral to society (241).

A key limitation of modeling studies is the assumption that people with undiagnosed diabetes will universally benefit from treatment after screen detection. This assumption may have led to optimistic cost-effectiveness ratios, which is especially pertinent given suggestions from recent trials that very tight glycemic control is not associated with macrovascular disease reduction (145–147). However, there are reasons to believe that tight glycemic control early in the disease course may be beneficial and relatively more cost-effective than when applied during later stages of the disease, as in the aforementioned trials. The population included in
trials of very tight glycemic control had long-standing disease and poor glycemic control prior to enrollment, and a substantial proportion of subjects already had established cardiovascular disease. Very tight glycemic control in such populations may have little or no effect on the long-term deleterious macrovascular effect of glycemia (242).

Two other points deserve mentioning: 1) very tight glycemic control was shown to be associated with microvascular benefits (243, 244); and 2) the possible lack of benefit in terms of macrovascular risk may not apply to earlier stages of the disease, as indicated by the 10-year results of the UKPDS trial (including people with recently diagnosed diabetes), which showed a long-term beneficial effect of tight glucose control on both macrovascular and microvascular outcomes (150). Most modeling studies addressing early detection and treatment of T2DM have used estimates from the UKPDS trial, and none have used estimates from the ACCORD, Veterans Affairs Diabetes Trial, and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trials (4, 226, 227, 229, 240).

Positive cost-effectiveness ratios in modeling studies were driven by both larger benefits and larger costs compared with no screening. However, cost-effectiveness ratios of screening policies are not the only element to account for in the decision-making process when considering adoption of screening policies. The opportunity costs will have to be factored in; consideration of costs related to the next-best choice of screening policy available among the mutually exclusive choices will play a crucial part in ensuring that "scarce" resources are used efficiently.

Screening intervals. There are no compelling data that can be used to decide the optimum frequency of screening for T2DM or dysglycemia. An optimal interval between screening rounds would be one at which the prevalence of undiagnosed cases reaches the prevalence of such cases at the previous screening, and the cost-effectiveness is the same for each screening (6). The annual rate of progression from IFG and IGT to diabetes is 5%–10% (54), which might argue for a short screening interval for people with dysglycemia. The annual progression from normoglycemia to diabetes, however, is in the range of 0.6%–1.2%, depending on the population and age group studied. In a simulation quantifying the proportion of false positives with screening by OGTT, the percentage was 47.5% for annual repeat screening and 33.9% for a screening interval of 3 years (245). The US-based simulation mentioned above reported that targeted screening for T2DM would be most cost-effective if repeated every 3–5 years (240). Currently, most professional organizations (246–250) recommend a 3-year screening for diabetes and/or dysglycemia for people at high risk.

Screening practices

In this review, we report on screening programs conducted after 1997, the year in which the most recent diagnostic criteria for T2DM were adopted (Table 5). Screening strategies have been community-based or opportunistic, universal or targeted; these approaches have been used alone or in combination. Screening yields are highly variable and dependent on the test(s) and cutoff(s) used. They also depend on the level of quality control and presence of adequate diagnostic resources in programs, as shown in an audit reporting the challenges to implement T2DM screening in United Kingdom primary care (251). Current evidence does not support universal screening; however, data from the United Kingdom indicate that any well-conducted targeted screening may come close to universal screening (65). Most professional organizations advocate a selective and opportunistic approach in high-risk populations (246–250).

CONCLUSION

This review indicates that there has been considerable progress in the field of screening for hyperglycemia in recent years. However, important gaps remain in our current knowledge to be filled.

There are many reasons to screen for hyperglycemic conditions. T2DM and hyperglycemic conditions, in general, are increasingly common worldwide. The natural history of T2DM includes recognizable prediabetic and long latent diabetic phases. Suitable, reliable, high-performance, and acceptable tests are available and can aid in detection of hyperglycemic conditions. Point-of-care testing for glucose or HbA1c, which is even simpler, less invasive, and more convenient, especially in low-resources areas, is being explored. Risk scores, especially the ones not requiring measures of blood glucose, also hold significant promise for identifying those at high risk. Testing for diabetes does not seem to be associated with adverse psychosocial consequences. There are accepted and cost-effective treatments for recognized T2DM, as well as for IFG/IGT. Economic models strongly support undertaking targeted screening for both dysglycemia and T2DM.

Several concerns exist with regard to screening for hyperglycemia; caution should therefore be exercised when considering a screening program. To our knowledge, no trial of screening has been published. Evidence on the efficacy of early treatment in people with screen-detected diabetes is indirect, originating from studies of people with recently, conventionally diagnosed diabetes. It is unclear whether individual or combined therapies, cost-effective for established diabetes, would be equally efficacious in screen-detected patients. It is unlikely that such evidence would ever be available because conducting a trial assessing treatment versus observation in screen-detected people with diabetes may be logistically challenging and viewed as unethical. However, testing the incremental benefit of tight glycemic control over current standards in a screen-detected population may provide more insight. Although lifestyle modification and/or metformin reduces the incidence of diabetes in people with IGT, whether these therapies alter cardiovascular outcomes is still unknown. Furthermore, challenges remain in translating the evidence for diabetes prevention into routine practice, although a number of avenues are being tested (252). More practical, reliable, and easily administered tests than fasting plasma glucose and/or OGTT to identify IFG/IGT on a large scale must still be developed. The psychosocial impact of labeling people with IFG/IGT is still unknown, as well as the long-term effect of
early identification of T2DM on patient self-efficacy and behavioral changes.

Implementing any policy to actively identify diabetes/dysglycemia cannot be viewed lightly; it highlights the problem of the availability of resources within health systems to carry out detection and to cope with managing an increasing number of new cases. Currently, most health systems deliver suboptimal diabetes care and do not have the orientation and resources to provide appropriate lifestyle or other preventive interventions. Screening policies would require strengthening the health care system to enhance the value of screening. These issues of health system capacity would greatly influence the screening interval and yield; the latter would also depend on the test(s) used, the population involved, and the prevalence of the conditions. Screening will be a huge undertaking for most health care systems and, if implemented poorly, could cause more harm than good.

The compelling evidence for diabetes prevention interventions for those with dysglycemia using lifestyle modification has prompted some European countries to initiate national or transnational primary prevention programs (194, 253–255). In such translation endeavors, delivery of primary prevention care in the clinical and/or community settings would require identifying high-risk individuals, with the consequential identification of individuals with undiagnosed diabetes. In practice, screening for diabetes (a secondary prevention effort) therefore appears inseparable from a high-risk primary prevention approach. Consideration of issues related to screening for hyperglycemic conditions within a unified or holistic framework for diabetes prevention may be the way forward.

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