

**Screening for Type 2 Diabetes to Prevent Vascular Complications:  
Updated Recommendations from the Canadian Task Force on Preventive  
Health Care**

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**Technical Report**

November 2003

## **BACKGROUND**

### **Rationale for the Review**

In 1994, the Canadian Task Force for Preventive Health Care (CTFPHC) reviewed the evidence regarding screening for diabetes. Given the poor sensitivity of the screening test and the lack of evidence for prevention of microvascular and macrovascular complications in patients with type 2 diabetes, the Task Force recommended against screening for diabetes in the absence of symptoms or risk factors (D recommendation) (Beaulieu, 1994). Since 1994 a number of studies have been published looking at prevention of diabetes complications in patients with type 2 diabetes, as well as primary prevention of diabetes. Therefore, the CTFPHC undertook to update this topic by drawing heavily on the recent United States Preventive Services Task Force (USPSTF) review of the evidence for screening asymptomatic people for type 2 diabetes to prevent cardiovascular events (Harris, 2003). That review was enhanced by the Canadian Task Force on Preventive Health Care : new literature on screening was incorporated, and a systematic review of the evidence related to the prevention of diabetes in people with impaired glucose tolerance was undertaken.

### **Burden of Illness**

According to the National Diabetes Surveillance System (NDSS) which is based on physician services data and hospitalization data, in 1998-99 the prevalence of diabetes mellitus (DM) in Canadians aged 20 years and older was 4.80 % or approximately 1,054,100 people. The prevalence increases with age, from 1.04% in Canadians aged 20-29, to 13.49 % in those 75 years or older. An estimated 40.6% of cases occurred in people aged 20 to 59 years (Diabetes in Canada 2002). It is estimated that type 2 diabetes accounts for more than 90% of diagnosed diabetes.

### **Complications and health outcomes**

Diabetes is characterized by chronic hyperglycaemia and the subsequent development of microvascular complications that can lead to blindness, end-stage renal disease, peripheral neuropathies and sexual dysfunction, as well as macrovascular disease associated with a 2-4 fold

increased risk of coronary heart disease, an increased risk of stroke and limb amputations. (Brownlee 2001; Kannel 1979; Pyorala 1987; Stamler 1993) At the time of clinical diagnosis the prevalence of retinopathy has been estimated to be between 10 and 37% (Harris 1992 and UKPDS 30 1998). In a study of newly diagnosed patients, 2% had had a myocardial infarct, 3% had angina and 1% had had a stroke (UKPDS 6 1990). Ten years following the diagnosis of diabetes greater than 20% of patients will have had a major cardiovascular event, less than 5% will have developed blindness, and under 2% will have developed end-stage renal disease or lower extremity amputation (Harris 2003).

10 In 1999, 2.6% of all deaths in Canada were attributed to diabetes. This is likely to be an underestimation since diabetes was listed as the cause of death in only 28% of people with diabetes even though they had died of diabetes-related illnesses such as kidney failure, heart disease or stroke (Health Canada 1998).

### **Economic Burden**

In Canada, the economic burden due to diabetes in 1993 was estimated to be \$1.7 billion. One quarter of those costs were attributable to the direct values of goods and services, while the remainder were due to lost production from illness, injury, disability or premature death (Moore 1997).

### 20 **Risk Factors for Type 2 Diabetes**

Diabetes is a chronic disease with multi-factorial causes involving the interaction of genetic susceptibility and environmental factors. Some are non-modifiable factors such as ethnicity, family history and age, but others such as overweight, obesity and lack of physical activity are potentially modifiable. Among individuals with self-reported diabetes in 1998, 74.3% were overweight and 65.1% reported that they were not physically active (compared to 55.4% of the general population) (Diabetes in Canada 2002). Type 2 diabetes also occurs more frequently in women with prior gestational diabetes, polycystic ovarian syndrome, and in people with hypertension and dyslipidemia. Smoking, excess consumption of alcohol and hypertension exacerbate the risk of complications from DM.

## **Special Populations**

A systematic review of the literature, carried out in 1994, determined that in the United States, nearly all minority groups had higher prevalence rates for DM than the white population. (Carter 1996). It is widely recognized that type 2 DM has become a serious health problem in various aboriginal groups around the world. In Canada, the prevalence of diabetes among First Nations is now at least 3 times the national average. The Aboriginal Peoples Survey, conducted across Canada in 1991, determined that 8.5% of North American Indian peoples on reserves or settlements had diabetes. The prevalence rate was lower in those living off reserve (5.3%). (Chapter 6, Diabetes in Canada 2002).

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## **Why Screen?**

The idea to screen for diabetes comes from the notion that approximately 50% of people with prevalent diabetes have not been diagnosed (Harris 1998). Data from the United Kingdom Diabetes Study suggested that patients are diagnosed either because of symptoms of hyperglycemia (i.e. polydipsia, polyuria, fatigue, blurry vision) (53.7%), infections (13%), because of a diabetes-related complication (2.1%), or through asymptomatic screening associated with the use of blood chemistry profiles done in other situations (i.e. pre-operative) (31.2%) (Colagiuri 2002).

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As depicted in Figure 1, it is believed that diabetes is manifest initially as a mild impairment in glucose tolerance by either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The impairment in glucose tolerance then progresses to overt diabetes, which is initially asymptomatic (point A). With a further impairment of glucose tolerance symptoms appear (point B) and the clinical diagnosis is made. The time between point A and point B can be called the 'preclinical phase' and is defined as the period during which the blood sugars are diagnostic of diabetes, however, patients remain asymptomatic and undiagnosed. The length of this preclinical phase has been estimated at 9-12 years (Harris 1992). Using this estimate, systematic screening would detect diabetes on average 5-6 years before discovery by clinical diagnosis (Harris 2003). One of the difficulties with these estimates comes from the variable way in which diabetes is diagnosed. Since most patients are discovered while being assessed for other conditions, the population advantage of systematic screening may be less.

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The CTF adopted the analytic framework used by the USPSTF in analyzing the diabetes screening literature. In approaching diabetes and its complications, the USPSTF came to regard diabetes as a vascular disease, with both microvascular and macrovascular complications. As in the general population, interventions to prevent macrovascular complications such as treatment of hypertension, hyperlipidemia and treatment with aspirin, were reviewed and examined in the context of those with diabetes, as well as the treatments specific to diabetes such as tight glycemic control. Similar treatments were looked at for the prevention of microvascular complications, however, the majority of the evidence for such prevention in the literature focused on the effects of tight glycemic control. In their approach to the important health outcomes, cardiovascular events, significant visual loss, end-stage renal disease and amputation were considered. Other outcomes such as progression of retinopathy and nephropathy were considered as intermediate outcomes. Finally, the USPSTF attempted to discern the added benefit of screening and diagnosing patients earlier than the usual clinical detection time. The objective of this review was to answer the following key questions:

**Key Question 1:** Is there direct RCT evidence 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?

## METHODS

Harris et al reviewed the literature from the USPSTF review of the same topic from 1996 and searched MEDLINE and the Cochrane library from January 1, 1994 to July 30 2002 (Harris 2003). The CTF updated a similar search of the literature from July 30, 2002 to Dec 31, 2002. No further articles meeting the inclusion criteria were found. The evidence was reviewed using the Canadian Task Force methods outlined in the Appendix.

## RESULTS

### 10 **Conclusions of the USPSTF regarding the Value and Yield of Screening Tools (Harris 2003)**

*Key Question 1. Is there direct RCT evidence that screening for diabetes improves health outcomes?*

No studies compared screening for diabetes with an unscreened population or examined 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?*

#### *a. Predictive Value of the Screening Tool*

20 The historical gold standard for the diagnosis of diabetes is the 2 hr post glucose load value (2 hr PG) of 11.1 mmol/L or more following a 75g oral glucose tolerance test (OGTT). In 1997 the American Diabetes Association suggested that a fasting plasma glucose (FPG) threshold of 7.0 mmol/L was an acceptable alternative to the 2 hr PG for the diagnosis of diabetes (Expert Committee 1997). Both of these criteria were chosen because they have been shown to reflect a threshold separating those subjects who are at substantially increased risk of microvascular complications (retinopathy) (Bennett 1976, McCance 1994, Engelgau 1997, The expert committee 2003). These thresholds do not do as well for prediction of macrovascular disease. While the FPG and 2 hr PG in the diabetes range are both strongly associated with coronary artery disease and all-cause mortality rates (Charles 1996), values below these levels are also

indicative of increased risk for macrovascular disease. Persons with impaired glucose tolerance (IGT) (2 hr PG between 7.8-11.0) also have a higher risk of cardiovascular events and mortality, than those with normal glucose tolerance (DECODE 1999, Coutinho 1999). In a meta-analysis that assessed the relationship between glucose and cardiovascular events in 95,783 persons, IGT was associated with a relative risk of 1.58 and impaired fasting glucose (IFG) with a risk of 1.33 for cardiac events (Coutinho 1999).

*b. Accuracy and Reliability of the Screening Tool*

10 Although the FPG required to diagnose DM has been lowered to 7.0 mmol/L to improve sensitivity, in studies of good to fair quality the FPG cutpoint of 7.0 mmol/L or more still had a sensitivity of only 40-87% to detect a 2 hr PG of 11.1 mmol/L, but a specificity of 96-99% (Blunt 1991 Lee 1997 Chang 1998 Wiener 1997). However as mentioned, the FPG of >7.0 mmol/L has been shown to be strongly associated with the prevalence of retinopathy (McCance 1994, Engelgau 1997, The expert committee). Lowering the FPG threshold further to 6.1 mmol/L would improve sensitivity (66-95%) at the cost of specificity (90-96%) (Engelgau 2000).

The random (postprandial) capillary glucose may be comparable to the FPG, depending on the cutpoint used. In one study, a random capillary glucose of 6.7 mmol/L or more had a sensitivity of 75%, with a specificity of 88% (Harris 2003).

20 In terms of reliability, the FPG appears to be more reproducible than the 2 hr- post glucose (PG). When adults were given the OGTT and it was repeated at 2 to 6 weeks, the intra-individual coefficients of variation were higher for the 2 hr PG than for the FPG (6.4% for FPG, 16.7% for 2 hr PG) (Mooy 1996).

While some studies have shown that frequency distributions for the diagnosis of diabetes using HbA1c are similar to those using FPG, and some studies have defined cutpoints above which microvascular disease is more likely, many different methods still exist for the measurement of HgA1c, making it difficult to assign an appropriate cutpoint (The Expert Committee).

*c. Other Screening Tools*

Three questionnaires have been studied as potential tools for screening asymptomatic people, the ADA questionnaire “Take the Test, Know the Score”, the NHANES questionnaire, and the Netherland’s Hoorn Study questionnaire. They were shown to have insufficient sensitivity (49-80%) to be used as a screening tool (Rolka 2001, Newman 1994).

*d. Prevalence of Undiagnosed Diabetes in the Population*

10 Data from the NHANES III in the United States showed that use of the FPG cutoff of 7.0 mmol/L or more yielded a DM prevalence of 4.35% in individuals 40-74 years of age without a medical history of diabetes (The Expert Committee 2003).

In summary, the fasting plasma glucose is currently considered the most acceptable test to diagnose diabetes in the asymptomatic patient. The cutpoint FPG of 7.0 mmol/L or more has only 40-87% sensitivity, but good specificity and is strongly associated with retinopathy. Macrovascular disease is associated with hyperglycemia, both below and above this cutpoint, with increasing risk associated with increasing values (Coutinho 1999). The OGTT, while considered the gold standard, is more costly and time-consuming than the FPG and less reliable.

20 **Conclusions of the USPSTF regarding Treatment Options to Prevent Significant Health Outcomes (Harris 2003)**

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?*

*Treatment of DM and Prevention of Significant Health Outcomes*

The health outcomes considered included death, cardiovascular events, significant visual loss, end-stage renal disease, and amputations. Since the largest mortality impact associated with diabetes is from cardiovascular events, a good deal of importance was placed on prevention of cardiovascular disease.

*a. Tight Glucose Control*

The review found that tight glucose control in the preclinical phase of diabetes was unlikely to lead to a large benefit. This conclusion was primarily drawn from the findings of a large RCT of good quality, which found that after 10 years of tight glucose control there was no significant difference in all-cause mortality (18.7% vs 17.9%  $p=0.44$ ), and no significant difference in diabetes-related death (death from MI, stroke, PVD, renal disease hyper- or hypoglycemia and sudden death). There was a reduction in myocardial infarction (RR 0.84 (95% CI 0.7-1.0), however this did not reach significance ( $p=0.052$ ) (UKPDS 33). A significant reduction in microvascular endpoints was also found, however this was primarily due to a reduction of retinal photocoagulation, which, given a trial where treatment was not blinded, may have been subject to bias. There was a significant reduction in progression of retinopathy, however there was no difference in deterioration of visual acuity or proportion of patients who became blind in both eyes. No significant difference in amputations, stroke, or renal failure was detected.

Four other RCTs were small and not sufficiently powered to find significant differences in many of the outcomes and found no significant difference in cardiovascular events. Only one study, a multifactorial intervention trial, showed a significant reduction in blindness in 1 eye, but no difference in visual acuity between groups (Gaede 1999).

*b. Tight Blood Pressure Control*

Aggressive treatment of blood pressure was found to lead to improved outcomes over conventional, less stringent, blood pressure goals in patients with diabetes. Earlier detection of diabetes would therefore change the blood pressure treatment target and presumably improve outcomes. This evidence was primarily drawn from 2 RCTs of fair quality. In a trial of patients with hypertension, subjects were randomized to one of three diastolic blood pressure goals ( $\leq 90$ , 85, or 80) and ASA or placebo (Hansson 1998). After 5 years, there was no significant benefit noted between the three blood pressure groups overall. However, in the patients with diabetes there were significantly more major cardiovascular events (RR 2.06 (1.24-3.44) and higher cardiovascular mortality (RR 3.0 (1.28-7.08)) in the  $\leq 90$  mm Hg group compared with the  $\leq 80$  mm Hg group.

In the UKPDS, patients with hypertension randomized to tight blood pressure control for 10 years had a significant reduction in diabetes related death (MI, sudden death, stroke, PVD and renal failure) (RR 0.68 (95% CI 0.49-0.94), as well as a significant reduction in risk of stroke (RR 0.56 (0.35-0.89)), any diabetes related end point 0.76 (0.62-0.92), risk of microvascular disease (aggregate clinical endpoint), and risk of retinal photocoagulation (UKPDS 38 1998). Two other smaller RCT's in diabetic patients given intensive blood pressure therapy showed a significant reduction in all-cause mortality in one (Estacio 2002), and a reduction in stroke in the other (Schrier 2002).

### 10 *c. Treatment of Hyperlipidemia*

Lipid-lowering treatment had a substantial benefit on cardiovascular outcomes and mortality in patients with diabetes and hyperlipidemia, regardless of low-density lipoprotein (LDL) cholesterol level in some studies. Several randomized controlled trials of primary and secondary cardiac prevention, using HMG-CoA reductase inhibitors (statins) and fibrates, have shown significant reductions in cardiovascular events in patients with diabetes and hyperlipidemia (relative risk reduction similar in both: 24-42%) treated over 5-6 years (Pyorala 1997; Koskinen 1992; Frick 1987; LIPID Study Group 1998; Downs 1998; Rubins 1999; Haffner 1999; Pignone 2001; MRC/BHF Heart Protection study 2002; Robins 2001; Goldberg 1998). In one fair study of primary prevention, use of bezafibrate in diabetic patients with mild hyperlipidemia reduced the incidence of myocardial infarction or ischemic changes on ECG by 20 69% (p=0.01) (Elkeles 1998). Although the relative risk reduction in primary prevention studies was similar in persons with and without diabetes, the absolute risk reduction would be larger in persons with diabetes given their baseline risk of cardiovascular disease is 2-4 times higher than non-diabetic persons.

Patients with diabetes appear to benefit even at low levels of LDL cholesterol. In a large RCT of patients with diabetes and non-diabetic patients considered at high risk for cardiovascular events (with or without previous cardiac disease), patients treated with simvastatin for 5 years had a significant decrease in overall mortality, primarily due to a decrease in cardiovascular deaths (RR 0.83 (0.75-0.91)) (MRC/BHF Heart Protection Study 2002). All 30 patients treated with simvastatin had a similar and significant proportional reduction in CHD

events including patients with diabetes and previous heart disease, as well as patients with diabetes but no previous coronary heart disease (first major coronary event: 5.5% on simvastatin vs 8.4% on placebo,  $p < 0.0001$ ). In a subgroup analysis, among all the 5963 patients with diabetes, the proportional risk reduction was about 25% irrespective of sex, age, or treatment for hypertension (MRC/BHF Heart Protection Study 2003). A similar reduction was seen even in patients with diabetes who presented with LDL levels below 3.0 mmol/L or total cholesterol below 5.0 mmol/L (27% reduction (13-40,  $p = 0.0007$ )) (MRC/BHF Heart Protection Study 2003). Even among the 1343 diabetic patients without known occlusive arterial disease whose pretreatment LDL cholesterol was below 3.0 mmol/L, there was a marginally significant 30% reduction in first major vascular events in patients on simvastatin ( $p = 0.05$ ) (MRC/BHF Heart Protection Study 2003). In an analysis of two secondary prevention trials, it was noted that in patients with LDL levels below 3.2 mmol/L, only the patients with diabetes benefited from statin therapy, whereas nondiabetic persons did not (Sacks 2002).

#### *d. Treatment with ASA*

The relative risk reduction seen in patients taking aspirin appears to be similar in patients with diabetes and without diabetes, and appears to be related to level of CV risk. In a meta-analysis of 145 RCT's using antiplatelet therapy for secondary prevention, diabetic subjects had approximately a 25% reduction in vascular events, a reduction similar to the non-diabetic subjects (Antiplatelet 1994). In a study of patients with hypertension, aspirin significantly reduced cardiovascular events by 15% ( $p = 0.03$ ) and myocardial infarction by 36% ( $p = 0.002$ ), with a similar RR seen in patients with and without diabetes. Similar results were seen in the Early Treatment Diabetic Retinopathy Study of patients with type 1 and type 2 diabetes, where 48% had previous CV disease. Aspirin decreased the RR for myocardial infarction to 0.72 (0.55-0.95) over 5 years. The USPSTF summary on aspirin for the primary prevention of cardiovascular events estimated that for 1000 patients with a 5% risk of CHD over 5 years, 6 to 20 myocardial infarctions would be prevented by aspirin use while 0 to 2 hemorrhagic strokes and 2 to 4 major GI bleeding events would be caused (USPSTF 2002). The net benefit of aspirin would increase with increasing cardiovascular risk.

*e. Counseling for Diet, Physical Activity and Smoking Cessation*

No studies were found that showed that the diagnosis of diabetes led to more effective outcomes in patients counseled to improve their diet, increase physical activity or stop smoking.

*f. Foot Care Programs*

Foot care programs given to patients with long-standing diabetes can reduce the risk for amputations (McCabe 1998; Litzelman 1993; Patout 2000) however, the risk of amputations in newly diagnosed patients or in patients within the first 10 years after diagnosis is low (Resnick 1999). Therefore, the benefit of counseling patients in the preclinical phase is unlikely to confer a large benefit.

**Overall USPSTF Perspective on Screening and Treatment of Type 2 Diabetes**

In summary, the USPSTF review concluded that the knowledge of diabetes in patients with hyperlipidemia and hypertension would lead to changes in treatment recommendations for blood pressure and lipid control, which in turn would reduce adverse cardiac outcomes over a 10 year horizon. This conclusion was dependent in part on the baseline level of cardiac risk of the patient, and in certain circumstances, it was the diagnosis of DM which increased the CV risk to a level worthy of intervention.

**20 Prevention of Progression from Impaired Glucose Values to Type 2 Diabetes**

*Key Question 4.* *What is the efficacy of lifestyle intervention for people with impaired fasting glucose or impaired glucose tolerance (IFG/IGT) in improving health outcomes?*

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are terms used to describe those who have glucose values above the normal range but do not meet the criteria for a diabetes diagnosis. Persons with both IGT and IFG have an increased risk of future diabetes (Unwin 2002, Edelstein 1997). Rates of progression to diabetes in persons with IGT range from around 4 to 9% per year (Edelstein 1997), and the average risk of diabetes with either IFG or IGT is around five times greater than those with normal glucose tolerance (Unwin 2002). These

intermediate conditions are not usually associated with diabetic renal, visual or neurologic complications, but they have been shown to increase one's risk of cardiovascular disease and mortality (DECODE 1999, Coutinho 1999, Meigs 1998, Bjornholt 1999, Balkau 1999, Saydah 2002, Khaw 2001, Barzilay 2001, Haffner 1990, McPhillips 1990, Harris 1998-1).

Because IGT and IFG are asymptomatic states, persons with these abnormalities can only be identified through screening. There is considerable debate regarding the best screening test, particularly since IGT requires a 2-hour OGTT, which is more time-consuming and cumbersome than the FPG. However, evidence suggests that the OGTT to detect IGT may be a better test to identify persons at risk for diabetes than the FPG. Although both conditions portend similar risks of future diabetes, persons with IGT comprise a larger high-risk group than those with IFG. IGT affects around 12-20% of adults, whereas 7-14% of persons have IFG (DECODE 1999, Nakagami 2002, Harris 1998-2). In addition prospective studies suggest that IGT is a more sensitive predictor of diabetes risk than is IFG, despite comparable specificities (Shaw 1999, McNeely 2003). Finally when the IFG category is compared to IGT, 90-96% of persons with IFG have co-existing IGT, but a normal fasting glucose misses an additional 57-76% of persons who have isolated IGT (Anand 2003, Amoah 2002, Metcalf 2000, Wahl 1998, Gimeno 1998, Devegt 1998). Even when the fasting glucose target is reduced to 5.3 mmol/L, only 60% of persons with IGT are detected with the FPG (Anand 2003). Therefore although the FPG may be useful to identify persons with IFG who are at risk for diabetes, a normal test may miss up to 40% of individuals with isolated IGT who remain at risk.

The potential benefit of screening for IFG and IGT depends on the availability of interventions to reduce diabetes outcomes. No studies have analyzed the impact of screening for these conditions on diabetes complications. However five randomized controlled trials have examined the effect of either intensive lifestyle or pharmacologic interventions in overweight persons with IGT on the incidence of diabetes (Pan 1997, Tuomilehto 2001, Knowler 2002, Chiasson 2002, Buchanan 2002), and one study also evaluated the incidence of cardiovascular events and hypertension as secondary outcomes (Chiasson 2003). Lifestyle intervention studies from China, Finland, and the US evaluated the benefits of programs providing regular individual counselling sessions on dietary and exercise advice, as well as physical activity training when necessary (Pan 1997, Tuomilehto 2001, Knowler 2002). Programs from the two larger studies were aimed at reducing and maintaining a 5-7% weight loss, through dietary changes and at least

20-30 minutes per day of exercise (Tuomilehto 2001, Knowler 2002). Despite a weight loss success rate of around 40%, these interventions resulted in a 42-58% reduction in progression to diabetes over 3-6 years.

The US study also assessed the benefit of metformin treatment in subjects with IGT, and they found a 31% reduction in incident diabetes over 3 years, which dropped to 25% after a 1 to 2-week period off the drug (Knowler 2003). It is unclear whether the blood glucose levels would have continued to rise if these patients were followed for a longer period. Acarbose has also been shown to reduce diabetes incidence by 25% over 3 years in persons with IGT (Chiasson 2002). In addition, this study recently reported a 49% reduction in cardiovascular events and a 34% reduction in hypertension with acarbose treatment in IGT patients (Chiasson 2003). This benefit was found despite the fact that 31% of the subjects taking acarbose discontinued their treatment early (versus 19% of those on placebo), as the outcomes were analyzed on an intention-to-treat basis. However, because of the high rate of intolerance to acarbose due to its known gastrointestinal side effects, its use in asymptomatic persons with IGT may be limited. Lastly, troglitazone has been shown to decrease progression to diabetes over 2 years by 55% in a group of women with a history of gestational diabetes (Buchanan 2002). Two clinical trials examining the effectiveness of other medications to prevent diabetes in IGT patients are currently underway: The DREAM study with rosiglitazone and ramipril, and the NAVIGATOR study using nateglinide and valsaran (Unwin 2002).

These trials provide good evidence that intensive lifestyle interventions, and possibly therapy with metformin and acarbose, can reduce the progression from IGT to diabetes in the short-term. There is also fair evidence that acarbose can reduce cardiovascular outcomes and hypertension in persons with IGT (Chiasson 2003). Regarding prevention of diabetes with medication, because the primary diabetes outcomes in the acarbose and metformin studies were evaluated while the subjects were taking the drugs (acarbose), or taken off for a very brief period (metformin), the ability of these agents to prevent versus simply mask new diabetes is unclear. These treatments may therefore have to be continued indefinitely to provide benefit, and the long-term safety of these agents in asymptomatic persons without diabetes is not known. Furthermore, the adverse effects of troglitazone and its withdrawal from the market preclude its use.

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

While few studies have examined the harmful effects of screening for diabetes, in those studies that looked at patients diagnosed through screening no decrease in quality of life has been found (Edleman 2002). Patients who are diagnosed clinically appear to benefit from intensive glycemic control with improved quality of life (UKPDS 37; Testa 1998 (JAMA); Testa 1998 (Diabetes Care)). No studies were found looking at the distress associated with disease labeling or loss of insurability however, treatment appears to be relatively safe. Treatment of hyperglycemia with oral hypoglycemic agents or insulin may lead to hypoglycemia, although episodes of severe hypoglycemia are infrequent (2.3% of patients on insulin and 0.6% of patients on OHA's in the UKPDS). ACE inhibitors and statins have low rates of serious adverse effects (Bradford 1994; Pierce 1990).

## **INTERPRETATION**

### **Canadian Task Force Interpretation of the Current Research Evidence**

Although there is no direct evidence that screening for type 2 diabetes in the general population improves health outcomes, certain high-risk groups such as those with hyperlipidemia and hypertension, may benefit from screening and treatment. Patients with asymptomatic disease in the preclinical phase can be reliably diagnosed through screening. Intensive therapy of blood pressure, and hyperlipidemia, as well as treatment with aspirin in patients with diabetes leads to improved health outcomes. Of those patients with diabetes discovered clinically, the benefits of tight glycemic control in the first 10 years were seen only in intermediate outcomes (i.e. decrease in progression of retinopathy and nephropathy), with a non-significant trend for lower MI rates. Therefore, clinical health outcomes such as death, CV events, blindness, ESRD and amputations were not reduced by 10 years of glucose-lowering treatment. With screened patients presumably the gain within the first 15 years would be similar or even less, given that their level of hyperglycemia would be milder in most cases. One would expect that the benefit may be translated into improved health outcomes in trials of longer duration. It is also possible

that improved health outcomes would be demonstrated if treatment were started sooner, however there is no evidence indicating this currently.

There is good evidence that patients with diabetes, hypertension, and/or hyperlipidemia treated for 5 years with intensive blood pressure control, lipid lowering agents, and aspirin have a reduction in cardiovascular events and mortality. Because of the significant benefit to CV events within 5 years of treatment, it is assumed that screened patients who would be diagnosed on average 5-6 years earlier, would also benefit. This is because knowledge of their diagnosis of diabetes would lead to tighter blood pressure control and more aggressive lipid therapy.

10 There is fair evidence that patients with diabetes (including those with previous cardiac disease) and normal lipids benefited from statin therapy, however, this benefit is likely related to overall level of cardiac risk.

Although there are studies suggesting a benefit of treating persons in the pre-diabetes stage of IGT to decrease diabetes progression and possibly cardiovascular disease, the evidence is still inadequate to recommend screening for IFG or IGT. However, screening for diabetes in certain contexts may nonetheless identify a number of persons with IGT. These patients should be treated with lifestyle interventions aimed at lowering weight and increasing exercise, as it may lower the incidence of diabetes. Furthermore, acarbose treatment can also be considered for these patients, as it has been shown to reduce cardiovascular outcomes and hypertension. It should be noted that the prevention trials were all between 3 and 6 years, and it is unclear  
20 whether the effects of lifestyle or pharmacologic interventions persist beyond that period. Furthermore, it is still uncertain whether diabetes can truly be prevented or whether these strategies simply delay its onset. The impact of delaying diabetes for a few years on preventing end-organ complications would likely be small, as complication risks are low in the first 15 years after diabetes diagnosis. The beneficial effects of lifestyle modification on cardiovascular events in persons with IGT also remain to be demonstrated. Finally, the cost-effectiveness of screening for IGT and offering lifestyle interventions only to those with a positive test, versus offering these programs to all persons with diabetes risk factors, has not been examined.

### **Canadian Task Force Recommendations (Table)**

1. There is fair evidence to recommend screening adults with hypertension for type 2 diabetes to reduce the incidence of CV events and mortality (Grade B recommendation).
2. There is fair evidence to recommend screening adults with hyperlipidemia for type 2 diabetes to reduce the incidence of CV events and mortality (Grade B recommendation).
3. There is good evidence to recommend treatment of overweight\* individuals with IGT with lifestyle interventions to reduce the incidence of diabetes progression (Grade B recommendation).
- 10 4. There is insufficient evidence to recommend treatment of overweight\* individuals with IGT with metformin or acarbose to reduce the incidence of diabetes progression (Grade I recommendation).
5. There is fair evidence to recommend treatment of overweight\* individuals with IGT with acarbose to prevent cardiovascular outcomes and hypertension (Grade B recommendation).

\*Body mass index (BMI, kg/m<sup>2</sup>) > 25 or > 22 in individuals of Asian descent

### **Clinical Considerations**

In patients who do not meet the above criteria, the decision to screen for diabetes or impaired glucose tolerance may be made on an individual basis. The decision to screen should hinge on an estimate of patients' overall cardiovascular risk. Patients whose overall risk would be raised by the diagnosis of diabetes to the extent that treatment would be changed, i.e. overall CVD risk is raised over 10%/year, may merit screening. Patients with other cardiac risk factors such as smoking, which put them at increased risk for cardiovascular disease, may benefit from screening for type 2 diabetes.

Screening involves only patients who are asymptomatic. Individuals who exhibit symptoms or signs of diabetes, or those who have potential complications associated with diabetes, should receive diagnostic testing.

Screening is best accomplished with a fasting glucose. The fasting glucose is more reliable and less cumbersome than the 75g OGTT, and has similar predictive value for the development of retinopathy as the 2 hr PG, but may miss some cases of diabetes. The diagnosis

can be made if the fasting glucose is  $\geq 7.0$  mmol/L, or the 2 hr PG is  $\geq 11.1$  mmol/L (Expert Committee for the diagnosis...2003). The test should be done on two occasions before a diagnosis can be made. The diagnosis of impaired fasting glucose is made if the fasting glucose is 6.1-6.9 mmol/L, and the diagnosis of impaired glucose tolerance is made if the 2 hr PG is 7.8-11.0 mmol/L following a 75g oral glucose tolerance test.

There is no information regarding the optimal screening frequency.

### **Recommendations of Others**

10 In its 2003 clinical practice guidelines the Canadian Diabetes Association recommends screening for diabetes using a fasting plasma glucose every 3 years in those 40 years of age and older (grade consensus) (Canadian Diabetes Association, 2003). It recommends that screening be considered at an earlier age or be performed more frequently, or both, using a fasting glucose or 2-hour OGTT in people with additional risk factors for diabetes (grade D, consensus).

The American Diabetes Association recommends patients, particularly those with a BMI = 25kg/m<sup>2</sup>, should be screened at 3-year intervals beginning at age 45, using a fasting glucose. They too suggest testing should be considered at an earlier age or be carried out more frequently in those who are overweight if additional diabetes risk factors are present.

20 The USPSTF found the evidence insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose (Grade I recommendation). They did, however, recommend screening for type 2 diabetes in adults with hypertension or hyperlipidemia (Grade B recommendation) (USPSTF recommendations and rationale 2003).

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### **Acknowledgements**

The Task Force thanks the following independent experts for reviewing a draft form of this report: Dr. Paul S. Frame, Dept. of Family Medicine, University of Rochester, Rochester, New York; Dr. Janet Hux, Dept. of Medicine, University of Toronto, Ontario. The views expressed in  
10 this report are those of the authors and the Canadian Task Force and do not necessarily reflect the positions of the independent reviewers.

The authors would like to thank Dr. Russell Harris for his valuable input, and Ruth Walton for her helpful assistance in preparing this manuscript.

## REFERENCES

- Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease NHANES III participants age 50 years and older. *Diabetes* 2003;52:1210-4.
- Amoah AGB. Undiagnosed diabetes and impaired glucose regulation in adult Ghanaians using the ADA and WHO diagnostic criteria. *Acta Diabetologica* 2002;39:7-13.
- Anand SS, Razak F, Vuksan V, Gerstein HC, Malmberg K, Yi Q, et al. Diagnostic strategies to detect glucose intolerance in a multiethnic population. *Diabetes Care* 2003;26:290-6.
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
- Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? *Diabetes Care* 1999;22:696-9.
- Barzilay JI, Spiekerman CF, Kuller LH, Burke GL, Bittner V, Gottdiener JS, et al. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care* 2001;24:1233-9.
- Beaulieu MD. Screening for diabetes in the non-pregnant adult. In: Canadian Task Force on Preventive Health Care. *The Canadian Guide to Clinical Preventive Health Care*. Ottawa: Canada Communication Group; 1994. p. 602-9.
- Bennett PH, Rushforth NB, Miller M, Lecompte PM. Epidemiologic studies of diabetes in Pima Indians. *Recent Prog Horm Res* 1976;32:333-76.
- Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care* 1999;22:45-9.
- Blunt BA, Barrett-Connor E, Wingard DL. Evaluation of fasting plasma glucose as a screening test for NIDDM in older adults. Ranco bernardo study. *Diabetes Care* 1991;14:989-93.
- Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, et al. Expanded Clinical Evaluation of Lovastatin (Excell) study results: two-year efficacy and safety follow-up. *Am J Cardiol* 1994;74:667-73.
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414(6865):813-20.
- Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, et al. Preservation of pancreatic  $\beta$ -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002;51:2796-803.

- Canadian Diabetes Association Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. Screening and prevention. *Can J Diabetes* 2003;27 (Suppl 2):S10-3.
- Carter JS, Pugh JA, Monterossa A. Non-insulin dependent diabetes mellitus in minorities in the Unites States. *Ann Intern Med* 1996;125:221-32.
- Chang CJ, Wu JS, Lu FH, Lee HL, Yang YC, Wen MJ. Fasting plasma glucose in screening for diabetes in the Taiwanese population. *Diabetes Care* 1998;21:1856-60.
- Charles MA, Balkau B, Vauzelle-Kervoeiden F, Thibult N, Eschwege E. Revision of diagnostic criteria for diabetes (Letter) *Lancet* 1996;348:1657-8.
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-7.
- Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290:486-94.
- Colagiuri S, Cull CA, Holman RR for the UKPDS Group. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcome? *Diabetes Care* 2002;25:1410-7.
- Colhoun HM, Thomason MJ, Mackness MI, Maton SM, Betteridge DJ, Durrington PN, et al. Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 2002 19(3):201-11.
- Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999;22(2):233-40.
- de Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance. *Diabetes Care* 1998;21:1686-90.
- Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.
- Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Impact of diabetes screening on quality of life. *Diabete Care* 2002;25:1022-6.

- Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, et al. Predictors of progression from impaired glucose tolerance to NIDDM: An analysis of six prospective studies. *Diabetes* 1997; 46:701-710.
- Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, et al. Cardiovascular outcomes in type2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 1998;21:641-8.
- Engelgau M, Narayan KNV, Herman W. Screening for type 2 diabetes. *Diabetes Care* 2000;23:1563-80.
- Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes; diagnostic criteria and performance revisited. *Diabetes Care* 1997;20:785-91.
- Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23 Suppl 2:B54-64.
- Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-45.
- Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with tyhpe 2 diabetes and microalibunminuria the Steno type 3 randomised trial. *Lancet* 1999;353:617-22.
- Gimeno SGA, Ferreira SRG, Franco LJ, Iunes M. Comparison of glucose tolerance categories according to World Health Organization and American Diabetes Association Diagnostic Criteria in a population-based study in Brazil. *Diabetes Care* 1998;21:1889-92.
- Goldberg RB, Mellies MJ, Sacks FM, Moy LA, Howard BV, Howard WJ, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels; subgroup analyses and the Cholesterol and Recurrent Events (CARE) trial. The CARE investigators. *Circulation* 1998;98:2513-9.
- Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, et al. Reduced coronary events in simvastatin-treated patents with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analysis in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;159:2661-7.
- Haffner SM, Stem MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 1990;263:2893-8.
- Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension:

- principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-62.
- Harris MI, Eastman RC. Is there a glycemc threshold for mortality risk? *Diabetes Care* 1998;21:331-3.
- Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the third national health and nutrition examination survey, 1988-1994. *Diabetes Care* 1998;21:518-24.
- Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population aged 20-74 yr. *Diabetes* 1987;36:523-34.
- Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992;15:815-9.
- Harris MI. Non-insulin-dependant diabetes mellitus I black and white Americans. *Diabetes Metab Rev* 1990;6:71-90.
- Harris R, Donahue K, Rathore SS, Frame P, Woolf SH, Lohr KN. Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2003;138(3):215-29.
- Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(3 Suppl):21-35.
- Health Canada. Diabetes in Canada. 2<sup>nd</sup> ed. Ottawa: Health Canada; 2002. Available from: URL: [http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/dic-dac2/english/01cover\\_e.html](http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/dic-dac2/english/01cover_e.html)
- Health Canada. Economic Burden of Illness in Canada, 1998. Catalogue. No. H21-136/1998. Ottawa: Health Canada; 2002. Available from: URL: <http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ebic-femc98/pdf/ebic1998.pdf>
- Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 1979;2:120-6.
- Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC- Norfolk). *BMJ* 2001;322:15-8.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. *Diabetes Care* 2003;26:977-80.

- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine* 2002;346:393-403.
- Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820-5.
- Lee CH, Rook Chong S. Evaluation of fasting plasma glucose as a screening test for diabetes mellitus in Singaporean adults. *Diabet Med* 1997;14:119-22.
- Leiter LA, Barr A, Belanger A, Lubin S, Ross SA, Tildesley HD, et al. Diabetes Screening in Canada (DIASCAN) Study: prevalence of undiagnosed diabetes and glucose intolerance in family physician offices. *Diabetes Care* 2001;24:1038-43.
- Litzelman DK, Slemenda CW, Langefield CD, Hays LM, Welch MA, Bild DE, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin dependent diabetes mellitus. A randomized controlled trial. *Ann Intern Med* 1993;119:36-41.
- McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. *Diabet Med* 1998;15:80-4.
- McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 1994;21;308(6940):1323-8.
- McNeely MJ, Boyko EJ, Leonetti DL, Kahn SE, Fujimoto WY. Comparison of a clinical model, the oral glucose tolerance test, and fasting glucose for prediction of type 2 diabetes risk in Japanese Americans. *Diabetes Care* 2003;26:758-63.
- McPhillips JB, Barrett-Connor E, Wingard DL. Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. *Am J Epidemiol* 1990;131:443-53.
- Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med* 1998;128:524-33.
- Metcalf PA, Scragg RKR. Comparison of WHO and ADA criteria for diagnosis of glucose status in adults. *Diabetes Research and Clinical Practice* 2000; 49:169-80.
- Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. In: Mogensen CE, ed. *The kidney and hypertension in diabetes mellitus*. 5th ed. Boston: Kluwer; 2000. p. 655-706.
- Moore R, Mao Y, Zhang J, Clarke K. *Economic Burden of Illness in Canada, 1993*. Ottawa: Canadian Public Health Association; 1997. Available from: URL: <http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ebic-femc93/index.html>

- Mooy JM, Grootenhuys PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, et al. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance test in a general Caucasian population; the Hoorn Study. *Diabetologia* 1996;39:298-305.
- MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Nakagami T, Qiao Q, Tuomilehto J. Cardiovascular risk profile assessment in glucose-intolerant individuals – an evaluation of the World Health Organization two-step strategy: the DECODA Study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia). *Diabetic Medicine* 2002;19:549-57.
- Newman WP, Nelson R, Scheer K. Community screening for diabetes: low detection rate in a low-risk population. *Diabetes Care* 1994;17:363-5.
- Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and diabetes study. *Diabetes Care* 1997;20:537-44.
- Patout CA Jr, Birke JA, Horswell R, Williams D, Cerise FP. Effectiveness of a comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African-American population. *Diabetes Care* 2000;23:1339-42.
- Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* 1990;264:71-5.
- Pignone MP, Phillips CJ, Atkins D, Teutsch SM, Mulrow CD, Lohr KN. Screening and treating adults for lipid disorders. *Am J Prev Med* 2001;20(Suppl 3):77-89.
- Pyorala K, Laakso M, Uusitupa M. Diabetes and atherosclerosis: an epidemiologic view. *Diabetes Metab Rev* 1987;3:463-524.
- Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care*. 1997;20:614-20.
- Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-89.
- Resnick HE, Valsania P, Phillips CL. Diabetes mellitus and nontraumatic lower extremity amputation in black and white Americans: The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1992. *Arch Intern Med* 1999;159:2470-5.
- Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;285:1585-91.

- Rolka DB, Narayan KM, Thompson TJ, Goldman D, Lindenmayer AJ, Alich K, et al. Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care* 2001;24:854-65.
- Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.
- Sacks FM, Tonkin AM, Craven T, Pfeffer MA, Shepherd J, Keech A, et al. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. *Circulation* 2002;105:1424-8.
- Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care* 2001;24:447-53.
- Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-97.
- Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet* 2003;361:1150-8.
- Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, et al. Impaired fasting glucose or impaired glucose tolerance: What best predicts future diabetes in Mauritius? *Diabetes Care* 1999;22:399-402.
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.
- Testa MA, Simonson DC, Turner RR. Valuing quality of life and improvements in glycemic control in people with type 2 diabetes mellitus. *Diabetes Care* 1998;21(Suppl 3):C44-52.
- Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998;280:1490-6.
- The DECODE study group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. European Diabetes Epidemiology Group. *Lancet* 1999;354:617-21.

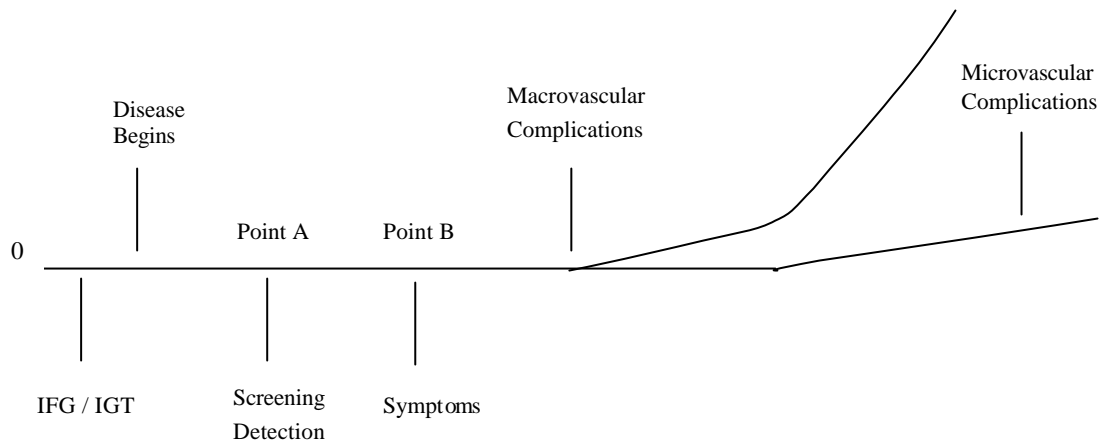
- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-97.
- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (ADA Position Paper) *Diabetes Care* 2003;26(1):S5-20.
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* 2001;344:1343-50.
- U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136:157-60.
- U.S. Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: recommendations and rationale. *Ann Intern Med* 2003;138(3):212-4.
- UK Prospective Diabetes Study Group. UKPDS 37. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control. *Diabetes Care* 1999;22:1125-36.
- UK Prospective Diabetes Study Group. UKPDS 30. Diabetic retinopathy at diagnosis of type 2 diabetes and associated risk factors. *Arch Ophthalmol* 1998;116:297-303.
- UK Prospective Diabetes Study Group. UKPDS 33. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837-53.
- UK Prospective Diabetes Study Group. UKPDS 38. Tight blood pressure control and risk for macrovascular and microvascular complications in type 2 diabetes. *BMJ* 1998;317:703-13.
- UK Prospective Diabetes Study Group. UKPDS 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Research* 1990;13:1-11.
- Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycemia: the current status on definition and intervention. *Diabetic Medicine* 2002;19:708-23.
- Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycemia: the current status on definition and intervention. *Diabetic Medicine* 2002; 19:708-23.

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Wahl PW, Savage PJ, Psaty BM, Orchard TJ, Robbins JA, Tracy RP. Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification. *Lancet* 1998;352:1012-5.

Wiener K. Fasting plasma glucose as a screening test for diabetes mellitus. *Diabet Med* 1997;14:711-2.

**Figure 1: Natural History of Type 2 Diabetes**



**Table: Summary of Recommendations**

Maneuver	Effectiveness	Level of Evidence <Refs>	Recommendations
Screening patients with hypertension for type 2 diabetes to reduce the incidence of cardiovascular (CV) events and CV mortality	CV events in patients with high blood pressure: RR 2.06 (1.24-3.44) CV deaths in patients with high blood pressure: RR 3.0 (1.28-7.08) Decrease in Diabetes Mellitus (DM) related deaths: RR 0.68 (0.49-0.94) Decrease in DM-related strokes: RR 0.56 (0.35-0.89)	Level I, fair <Harris 1998, UKPDS 38 1998, Schrier 2002, Estacio 2002>	The CTF concludes that there is fair evidence to recommend screening patients with hypertension for type 2 diabetes to reduce the incidence of CV events and CV mortality ( <b>B Recommendation</b> ).
Screening patients with hyperlipidemia for type 2 diabetes to reduce the incidence of CV events	RRR 24-42% in CV events	Level I, good <Pyorala 1997, Koskinen 1992, Frick 1987, LIPID Study Group 1998, Downs 1998, Rubins 1999, Haffner 1999, Pignone 2001, MRC/BHF Heart Protection study 2002, Robins 2001, Goldberg 1998>	The CTF concludes that there is fair evidence to recommend screening patients with hyperlipidemia for type 2 diabetes to reduce the incidence of CV events ( <b>B Recommendation</b> ).
Treating overweight* people with IGT with lifestyle intervention to reduce the incidence of diabetes progression.	Decreased progression to diabetes 42-58%	Level I, good <Pan 1997, Tuomilehto 2001, Knowler 2002>	The CTF concludes that there is good evidence to recommend treatment of IGT with lifestyle interventions to reduce the incidence of diabetes progression ( <b>B Recommendation</b> ).
Treating overweight* people with IGT with acarbose or metformin to reduce diabetes progression.	Metformin 25-31% reduction in diabetes Acarbose 25% reduction in diabetes	Level I, fair <Chiasson 2002, Knowler 2002, Knowler 2003>	The CTF concludes that there is insufficient evidence to recommend treatment of IGT with metformin or acarbose to reduce the incidence of diabetes progression ( <b>I Recommendation</b> ).
Treating overweight* people with IGT with acarbose to reduce CV events and hypertension.	49% reduction in CV events 34% reduction in hypertension	Level I, fair <Chiasson 2003>	The CTF concludes that there is fair evidence to recommend treatment of IGT with acarbose to prevent CV events or hypertension ( <b>B Recommendation</b> ).

\*Body mass index (BMI, kg/m<sup>2</sup>) > 25 or > 22 in individuals of Asian descent

<b>Appendix: Methodology of the Canadian Task Force on Preventive Health Care</b>	
<p><i>Critical appraisal</i></p> <p>The Task Force reviewed 1) the initial analytic framework and key questions for the proposed review; 2) the subsequent draft(s) of the complete manuscript providing critical appraisal of the evidence prepared by the lead authors, including identification and double, independent critical appraisal of key studies or recent systematic reviews, and ratings of the quality of this evidence using the task force's established methodological hierarchy (sidebar); and 3) a summary of the evidence and proposed recommendations.</p> <p><i>Consensus development</i></p> <p>Evidence for this topic was presented by the lead author(s) and deliberated upon during task force meetings in February, June, and October 2003. Expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead author were discussed, as were issues related to clarification of the recommendations for clinical application and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The group and lead author(s) arrived at final decisions on recommendations unanimously.</p> <p>Subsequent to the meetings, the lead authors revised the manuscript accordingly. After final revision, the Task Force sent the manuscript to # experts in the field (identified by Task Force members at the meeting). Feedback from these experts was incorporated into a subsequent draft of the manuscript.</p> <p>Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the task force methodology were maintained at all stages during review development, the consensus process and beyond to ensure uniformity and impartiality throughout.</p>	<p><b>Levels of evidence</b></p> <p><b>A. Research design rating:</b></p> <p><b>I</b> Evidence from randomized controlled trial(s)</p> <p><b>II-1</b> Evidence from controlled trial(s) without randomization</p> <p><b>II-2</b> Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group</p> <p><b>II-3</b> Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here</p> <p><b>III</b> Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees</p>
	<p><b>B. Quality (internal validity) rating (see Harris et al., 2001):</b></p> <p><b>Good</b> A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.</p> <p><b>Fair</b> A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known “fatal flaw”.</p> <p><b>Poor</b> A study (including meta-analyses or systematic reviews) that has at least one design-specific* “fatal flaw”, or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.</p>
	<p>*General design specific criteria are outlined in Harris et al., 2001. Inclusion/exclusion criteria are detailed in the Methods section.</p>
	<p><b>Recommendations Grades for Specific Clinical Preventive Actions</b></p> <p><b>A</b> The CTF concludes that there is <b>good</b> evidence to recommend the clinical preventive action.</p> <p><b>B</b> The CTF concludes that there is <b>fair</b> evidence to recommend the clinical preventive action.</p> <p><b>C</b> The CTF concludes that the existing evidence is <b>conflicting</b> and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.</p> <p><b>D</b> The CTF concludes that there is <b>fair</b> evidence to recommend against the clinical preventive action.</p> <p><b>E</b> The CTF concludes that there is <b>good</b> evidence to recommend against the clinical preventive action.</p> <p><b>I</b> The CTF concludes that there is <b>insufficient</b> evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.</p>
	<p><i>The CTF recognizes that in many cases patient specific factors need to be considered and discussed, such as the value the patient places on the clinical preventive action; its possible positive and negative outcomes; and the context and/or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.</i></p>