



Prediction and prevention of type 2 diabetes mellitus

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INTRODUCTION — Type 2 diabetes mellitus (DM) is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. Although the lifetime risk of type 2 diabetes is high, our ability to predict and prevent type 2 diabetes in the general population is limited. However, subjects at high-risk, including those with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), obesity, close relatives with type 2 diabetes, or who are members of certain ethnic groups (Asian, Hispanic, black), are appropriate candidates for preventive interventions [1]. (See "[Risk factors for type 2 diabetes mellitus](#)").

The goals of diabetes prevention are delaying the onset of diabetes, preserving beta cell function, and preventing or delaying microvascular and perhaps cardiovascular complications. Of these, preservation of beta cell function may be more important, as beta cell failure largely underlies the transition from pre-diabetic states to diabetes (as well as worsening of glycemic control once diabetes has developed). The individuals demonstrably at highest risk for development of diabetes include those with IFG, IGT, and especially those with combined IFG and IGT [2].

GLUCOSE TOLERANCE STATES AS PREDICTORS OF DM — Abnormal glucose metabolism can be documented years before the onset of overt diabetes. In some groups, insulin resistance appears to be the best predictor of future type 2 diabetes [3], but tests for insulin resistance are not practical in routine clinical practice. Other studies suggest that abnormalities of insulin secretion may precede the development of insulin resistance [4-6].

Impaired glucose tolerance — The term impaired glucose tolerance (IGT) describes subjects who, during an oral glucose tolerance test (OGTT), have blood glucose values between those in normal subjects and those in patients with overt diabetes (140 to 199 mg/dL [7.8 to 11.0 mmol/L]) ([show table 1](#)). IGT is also called pre-diabetes. The criteria for defining diabetes and pre-diabetes are reviewed in greater detail separately. (See "[Diagnosis of diabetes mellitus](#)").

Subjects who have only IGT do not develop the microvascular complications of diabetes such as retinopathy and nephropathy. They are, however, at substantially increased risk (when compared with matched subjects with normal glucose tolerance) for developing macrovascular disease (such as coronary artery disease) and for progression to type 2 diabetes [7-11]. In addition, a study of 980 elderly nondiabetic Finnish subjects followed for 3.5 years found that persistent IGT was associated with mildly impaired cognitive function [12].

The rate of progression from IGT to overt diabetes varies among different populations. In six

prospective studies, for example, the incidence rates of type 2 diabetes among patients with IGT ranged from 36 to 87 per 1000 person-years [13]. The rates were higher among Hispanic, Pima, and Nauruan people than among whites. Estimates of obesity (including body mass index, waist-to-hip ratio, and waist circumference) were positively associated with the incidence of type 2 diabetes (see below). In contrast, sex and family history of diabetes were not related to the rate of progression in most studies.

Impaired fasting glucose — Impaired fasting glucose (IFG) is defined as a fasting blood sugar of 100 to 125 mg/dl (5.6 to 7.0 mmol/L) (show table 1). IFG, also called pre-diabetes, increases the risk of developing type 2 diabetes [14].

Although fasting glucose levels less than 100 mg/ml (5.55 mmol/L) are considered normal by the 2003 criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, subjects with fasting glucose values in the higher quintiles of normal range are also at increased risk for developing type 2 diabetes. In a prospective cohort study (over 46,500 subjects followed for a mean of 81 months), the overall incidence of diabetes in those with normal fasting glucose was low (4 percent) [15]. However, there was an increased risk of diabetes incidence in those with fasting plasma glucose of 95 to 99 mg/dL (5.3 to 5.5 mmol/L) compared to <85 mg/dL (4.7 mmol/L) (hazard ratio [HR] 2.33, 95% CI 1.95 to 2.79) [15].

Similar results were reported in a study of 13,163 healthy male Israeli army recruits [16]. There was a progressive increased risk of diabetes for those with fasting plasma glucose levels greater than 87 mg/dl (4.83 mmol/l) compared with those in the lowest quintile with fasting glucose levels less than 81 mg/dl (4.5 mmol/l). The risk of diabetes was even greater (HR 8.23, 95% CI 3.6 to 19.0) in those with high normal glucose levels (91 to 99 mg/dL) in combination with elevated serum triglycerides (greater than 150 mg/dl) and elevated body mass index (>30), and may indicate subjects for whom preventive measures would be most effective.

IGT and IFG — Although the natural history of IFG and IGT is variable, approximately 25 percent of subjects with either will progress to diabetes over three to five years [2]. Subjects with additional diabetes risk factors, including obesity and family history, are more likely to develop diabetes.

The finding that some individuals have isolated IGT or IFG, suggests that there are different pathophysiologic mechanisms causing the abnormalities in glucose homeostasis [2]. Individuals with isolated IFG have hepatic insulin resistance, whereas those with isolated IGT predominantly have muscle insulin resistance and normal or slightly reduced hepatic insulin sensitivity. Subjects with abnormalities in both tests have hepatic and muscle insulin resistance, which confers an increased risk of progressing to diabetes compared with having only one abnormality.

Hemoglobin A1C — Although hemoglobin A1C (A1C) measurements are not currently recommended to diagnose diabetes, they may be helpful in predicting diabetes and targeting patients for intensive intervention. In one prospective study, patients with IFG and A1C \geq 5.9 percent had a 50 percent risk of progression to diabetes within six years [17]. In another prospective cohort study of 26,563 women followed for 10 years, baseline A1C level was an independent predictor of type 2 diabetes, even at levels considered to be within the normal range [18]. In those individuals with baseline A1C in the highest quintile (A1C >5.22), the adjusted

relative risk of diabetes was 8.2, 95% CI 6.0 to 11.1.

PREDICTION MODELS — There are several diabetes-prediction models that incorporate clinical risk factors and/or metabolic factors to generate a prediction score [19-25]. These models vary in complexity and most have not been validated in diverse populations.

Simple clinical models may be more effective in predicting diabetes than complex models [20,26]. As an example, in the Framingham Offspring Study, several models to predict incident diabetes were compared [26]. The simple clinical model included information typically available at clinic evaluations, such as age, parental history of diabetes, BMI, blood pressure, HDL, triglycerides, and impaired fasting glucose. Each of the metabolic syndrome traits (elevated blood pressure and triglyceride concentrations, low HDL levels, and impaired fasting glucose), obesity, and parental history were highly associated with developing diabetes. Adding more complex measurements (oral glucose tolerance, insulin sensitivity, insulin resistance) did not improve the model, nor did adding a genotype score based upon the presence of a number of risk alleles confirmed to be associated with type 2 diabetes [27].

In other models, the addition of genetic data to the simple clinical model (and other clinical models) had a minimal effect on prediction of type 2 diabetes [28,29]. In one such model, genetic data were incorporated based upon low and high genetic risk groups (quintiles with the lowest and highest number of risk alleles, respectively) [28]. The improvement in prediction was too small to allow for individual risk prediction. Thus, at the current time, there is insufficient evidence to support genotyping for risk assessment in clinical practice.

The genetics of type 2 diabetes, including a discussion of the risk alleles confirmed to be associated with it, are reviewed elsewhere. ([See "Pathogenesis of type 2 diabetes mellitus", section on Genetic susceptibility](#)).

PREVENTION — Three factors have been evaluated in an attempt to prevent type 2 diabetes: exercise, weight loss, and drug therapy. Smoking cessation may also be important. Intensive lifestyle intervention provides the greatest benefit in prevention of diabetes.

LIFESTYLE MODIFICATION

Diet — There are few trials that examine the effects of diet alone for the prevention of diabetes [30]. In one such trial, the Women's Health Initiative Dietary Modification Trial (WHI DMT), over 48,000 postmenopausal women (mean age 62 years), not specifically at high risk for developing diabetes, were randomly assigned to a low-fat diet (20 percent of caloric intake) or to a usual diet [31]. Weight loss and exercise were not part of the intervention.

After eight years of follow-up, there was no difference in the self-reported incidence of diabetes (approximately 7 percent in each group, HR 0.96, 95% CI 0.9-1.0). The difference in weight between the two groups was less than 2 kg. These results, which suffer from the absence of uniform glucose testing in the study, suggest that in average risk women, weight reduction, rather than changes in macronutrient composition, is more important for diabetes prevention. ([See "Weight loss/lifestyle intervention" below](#)).

Exercise — Although insulin resistance and impaired insulin secretion in type 2 diabetes have a substantial genetic component, they can also be influenced, both positively and negatively, by environmental and behavioral factors. The benefit of exercise in preventing diabetes has been demonstrated in several studies [32-37].

A meta-analysis of 10 prospective cohort studies of physical activity and type 2 diabetes reported a lower risk of developing diabetes with regular moderate physical activity, including brisk walking, compared with being sedentary (RR 0.69, 95% CI 0.58-0.83) [38]. The benefits persisted after adjustment for BMI, suggesting an independent effect of exercise on glucose metabolism. (See "[Effects of exercise in diabetes mellitus in adults](#)" for a discussion of the changes in glucose metabolism that can occur).

Weight loss/lifestyle intervention — Weight reduction, if sustained, can substantially improve glycemic control in patients with type 2 diabetes. (See "[Nutritional considerations in type 2 diabetes mellitus](#)"). There is also evidence that lifestyle intervention (combined diet and exercise) can improve glucose tolerance and prevent progression from IGT to type 2 diabetes, as illustrated by a meta-analysis of eight trials comparing exercise plus diet with standard therapy (RR with intervention compared to control 0.63, 95% CI 0.49-0.79) [39].

Finnish Diabetes Prevention Study — The Finnish Diabetes Prevention Study randomly assigned 522 middle-aged patients with impaired glucose tolerance (mean age 55 years, mean BMI 33.2 kg/m²) to a weight-reduction and exercise program or a control group [40].

- The mean weight loss in the intervention group was 3.5 kg at the end of two years compared with 0.8 kg in the control group. At the end of four years, the cumulative incidence of diabetes was significantly lower in the intervention group (11 versus 23 percent).
- The effect of the original lifestyle intervention appears to persist for at least three years after the end of the study. Patients who were diabetes-free at four years were followed for an additional three years [41]. No further lifestyle intervention was provided through the study during the extended follow-up. The reduction in diabetes incidence associated with the original intensive lifestyle group continued, although not as powerfully during the three-year follow-up (58 percent reduction during the trial; 36 percent reduction during the three-year follow-up). Over the extended seven-year follow-up, comparing intervention and control groups, the hazard ratio for diabetes was 0.57 (95% CI 0.43-0.76), with cumulative incidence of diabetes 23 versus 38 percent at the end of year six (43 percent reduction over the entire period).
- Patients who were homozygous for a polymorphism of the hepatic lipase gene (56 percent of subjects) were less likely to benefit from the lifestyle intervention, and therefore were more likely to develop diabetes (13 versus 1 percent in subjects who had at least one normal allele) [42].

Diabetes Prevention Program — The results of a second trial, the Diabetes Prevention Program (DPP), were similar [36]. In this trial, 3234 obese (average body mass index 34 kg/m²) subjects aged 25 to 85 years (average 51) at high risk for diabetes (based on BMI \geq 24 kg/m², and fasting and 2 hour plasma glucose concentrations of 96 to 125 mg/dL [5.3 to 6.9 mmol/L]

and 140 to 199 mg/dL [7.8 to 11.1 mmol/L], respectively) were randomly assigned to one of the following groups:

- Intensive lifestyle changes with the aim of reducing weight by 7 percent through a low-fat diet and exercise for 150 minutes per week. Details of the lifestyle intervention have been published [43].
- Treatment with [metformin](#) (850 mg BID) plus information on diet and exercise
- Placebo plus information on diet and exercise

The study was terminated one year ahead of schedule when the independent data safety monitoring board determined that the study hypotheses had been answered: The intensive lifestyle and [metformin](#) interventions reduced the cumulative incidence of diabetes by 58 and 31 percent, respectively.

The diet and exercise group lost an average of 15 pounds (6.8 kg) (7 percent) of weight in the first year, most of which was sustained for the duration of the study. At an average follow-up of three years, fewer patients in this group developed diabetes (14 versus 22 and 29 percent in the [metformin](#) and placebo groups, respectively). Lifestyle intervention was effective in men and women in all age groups and in all ethnic groups.

An analysis of patients in the intensive lifestyle group found that, within the three components of the intervention (weight loss, diet change, and exercise), diabetes prevention correlated most strongly with weight loss; there was a 16 percent reduction in diabetes risk for every kilogram reduction in weight [44]. Improvements in insulin sensitivity and insulin secretion, greatest in the intensive lifestyle intervention group, and somewhat lower in the [metformin](#) group, correlated directly with decreased risk of diabetes [45].

In contrast to the findings in the entire DPP cohort (lifestyle intervention more effective than [metformin](#) therapy), metformin and lifestyle intervention were similarly effective in reducing the incidence of diabetes in women with a history of gestational diabetes (GDM) [46]. In a preplanned subset analysis of women with a history of GDM and IGT, the incidence of diabetes was reduced by 50 and 53 percent in subjects assigned to metformin and lifestyle intervention, respectively, compared with placebo. In parous women with IGT and without a history of GDM, risk reductions with metformin and lifestyle (compared with placebo) were 14 and 49 percent, respectively.

The discrepancy is due, in part, to the higher cumulative incidence of diabetes during the three-year trial in women assigned to placebo with GDM versus no GDM (38.4 versus 25.7 percent) and in part due to the inability of women with a history of GDM randomly assigned to intensive lifestyle intervention to sustain physical activity and maintain weight loss.

Thus, both lifestyle interventions and [metformin](#) therapy are effective prevention strategies (with similar efficacy in the subset of women with a history of gestational diabetes), but the DPP lifestyle intervention may be impractical to implement on a national level. Long-term compliance with dietary interventions in the non-study setting has been poor, and new strategies, like those used in the DPP, need to be identified to promote cost-effective, long-term weight loss. ([See "Dietary therapy for obesity"](#)).

China Da Qing Diabetes Prevention Study — Lifestyle intervention was also effective among Chinese people with impaired glucose tolerance. In the China Da Qing Diabetes Prevention Study (CDQDPS), 577 adults with impaired glucose tolerance were randomly assigned, based on the clinic they attended, to a control group or to one of three active intervention groups (diet, exercise, or diet plus exercise) [47]. After six years, diabetes incidence was 31, 46, and 42 percent lower than in the control group for diet, exercise, and combined interventions, respectively.

The effect of the original lifestyle intervention appeared to persist after the end of the study, as illustrated by a follow-up study twenty years later (follow-up information, largely historical in nature, was obtained for 98 percent of participants) [48]. Those originally assigned to an active intervention group had a lower cumulative incidence of diabetes than the control group (80 versus 93 percent, respectively, with a risk reduction of 43 percent [HR 0.57, 95% CI 0.41-0.81]).

Epidemiologic analyses — In a post hoc analysis of MRFIT, a large, randomized primary prevention trial of intervention (consisting of advice on diet, exercise, stopping smoking, and more intensive blood pressure treatment) versus usual care in men at high risk for coronary heart disease [49]. In subjects with normal glucose tolerance at baseline (n = 11,827), the intervention program was associated with a lower risk of type 2 diabetes in the nonsmokers (HR 0.82, 95% CI 0.68-0.98), but not in the smokers. The lack of benefit among baseline smokers was thought to be due, in part, to weight gain that occurred with smoking cessation, in contrast to other studies that have reported a beneficial effect of smoking cessation on prevention of diabetes. ([See "Smoking" below](#)).

The combined effects of diet and healthy lifestyle also were important in preventing type 2 diabetes in women. Almost 90 percent of the cases of diabetes in the Nurses' Health Study were found in women with obesity, lack of exercise, a poor diet, and smoking, suggesting that many cases of diabetes could be prevented with a healthier lifestyle [50]. The relative risk of developing type 2 diabetes compared with normal weight physically active women was greatest in those who were both obese and inactive (RR 16.8, 95% CI 14-20), moderate for women who were active but obese (RR 10.7, 95% CI 8.7-13.1), and lowest for women who were lean but inactive (RR 2.1, 95% CI 1.7-2.6) [51]. Body mass index was also a stronger predictor of type 2 diabetes than physical activity in another cohort of women [52].

Summary — Changes in lifestyle, including diet modification, weight loss, and exercise slow progression of impaired glucose tolerance to overt diabetes. The beneficial effects of such intervention appear to continue after the original intervention. The importance of factors such as diet, body weight, and exercise can also be inferred from the findings in certain societies that have undergone rapid change towards a westernized lifestyle. In these societies, the prevalence of IGT and type 2 diabetes often increase greatly, correlated with both weight gain and decreased physical activity [53,54].

Smoking — Several large prospective studies have raised the possibility that cigarette smoking increases the risk of type 2 diabetes. ([See "Risk factors for type 2 diabetes mellitus"](#), section on Smoking).

A prospective study of 7735 men aged 40 to 59 years examined the impact of smoking cessation

on diabetes risk [55]. The benefit of smoking cessation was apparent five years after cessation, and the risk reverted to that of never smokers after 20 years.

While a causal association is plausible, an alternative explanation is that smokers have other habits that increase their risk for diabetes (such as exercising less or eating a less healthy diet).

Moderate intensity exercise, weight loss and smoking cessation are recommended for all individuals with IGT or IFG.

PHARMACOLOGIC THERAPY — Drug therapy may be helpful in preventing type 2 diabetes in high-risk patients for whom lifestyle interventions fail or are not sustainable. A number of drug classes have been studied. One systematic review and a meta-analysis of randomized controlled studies showed significant decrease in diabetes incidence with oral hypoglycemics and [orlistat](#) [56,57]. In the systematic review, evidence for the effectiveness of statins, fibrates, estrogen, and antihypertensive drugs in preventing diabetes were conflicting and limited to secondary analyses in cohort studies [56].

It is not clear whether the apparent effectiveness of some drug therapies is in delaying, rather than preventing, the onset of diabetes. Lifestyle changes, which are at least as effective and cheaper, are considered first line preventive therapy [57]. Longer follow-up studies (at least 10 years) of pharmacologic therapy with demonstration of reduced morbidity and mortality are needed before these drugs can be recommended for the majority of patients at high risk for diabetes.

In the meantime, [metformin](#), thiazolidinediones, and alpha-glucosidase inhibitors have demonstrated preventive efficacy. However, thiazolidinediones are limited by adverse effects and cost, and alpha-glucosidase inhibitors by gastrointestinal side effects and poor long-term compliance. Metformin is relatively inexpensive and safe and is especially effective in younger, more obese individuals [58]; its use is reasonable in the highest risk patients (see below and [show table 2](#)).

Metformin — [Metformin](#) appears to be effective in reducing the risk of type 2 diabetes in patients with IGT, although it is less effective than diet and exercise. This was illustrated in the Diabetes Prevention Program of obese patients with IGT described above [36]. Metformin reduced the rate of progression to diabetes (22 versus 29 percent with placebo at an average follow-up of three years). Metformin was effective in men and women and in all ethnic groups, but was relatively ineffective in older patients and in those who were less overweight.

In addition, a meta-analysis of randomized trials of [metformin](#) for the prevention of diabetes in individuals at high risk for diabetes showed that metformin decreased new-onset diabetes compared with placebo (odds ratio 0.6, 95% CI 0.5-0.8) [59]. Additional benefits of metformin included reductions in fasting blood sugar, fasting insulin, and modest improvements in body mass index, HDL, LDL, and triglycerides.

There has been concern that the diabetes prevention benefit of [metformin](#) might represent a "masking" of the development of diabetes rather than true prevention, since follow-up OGTTs in most studies were done while patients were still taking the medication. In one follow-up study of

1247 subjects in the DPP metformin group (who had not developed diabetes), follow-up OGTTs after stopping metformin (on average 11 days) showed that about 75 percent of the metformin benefit persisted [60]. Although the authors suggested that this finding is consistent with prevention, longer drug-free trials are needed to firmly draw this conclusion.

Although [metformin](#) is less effective than lifestyle intervention, the DPP study demonstrated a beneficial effect in reducing the risk of diabetes in younger, obese subjects, and particularly in women with a history of gestational diabetes [46]. In addition, metformin is relatively inexpensive and has no long-term serious side effects. Thus, the ADA recommends consideration of metformin for diabetes prevention in individuals with confirmed IFG and IGT who are less than 60 years of age and with a BMI >35 kg/m² [2]. Other individuals with IGT and IFG who may be candidates for metformin include those with additional risk factors for diabetes, such as a family history, elevated triglycerides, reduced HDL, hypertension, and an A1C >6.0 percent ([show table 2](#)).

Thiazolidinediones — The thiazolidinediones ([rosiglitazone](#) and [pioglitazone](#)) improve glucose utilization by muscle, decrease hepatic glucose production, and increase insulin secretion, at least in patients with IGT. Their efficacy in preventing type 2 diabetes in patients at risk, at least while therapy is continued, is suggested in several trials [61-63]. The use of these drugs in the management of type 2 diabetes is discussed elsewhere. ([See "Thiazolidinediones in the treatment of diabetes mellitus"](#)).

Troglitazone — The efficacy of the thiazolidinediones for the prevention of type 2 diabetes while therapy is still being given was shown in the TRIPOD trial (Troglitazone in Prevention of Diabetes), in which 266 Hispanic women with previous gestational diabetes were randomly assigned to receive troglitazone (400 mg/day) or placebo for a median of 30 months [61]. The annual incidence of diabetes was 5.4 and 12.1 percent in the troglitazone and placebo groups, respectively. Troglitazone, which has been withdrawn from the market in the United States and United Kingdom, also improved insulin sensitivity with an associated reduction in the acute (or first-phase) insulin response to glucose, indicating a reduction in the secretory demands placed on the beta-cells.

Troglitazone was also one of the treatment arms in the Diabetes Prevention Program (DPP), but the arm was discontinued because of safety concerns. However, those patients who had been on troglitazone were significantly less likely to develop diabetes [62].

Rosiglitazone — The Diabetes Reduction Assessment with [Ramipril](#) and [Rosiglitazone](#) Medication (DREAM) trial assessed the ability of rosiglitazone 8 mg daily to delay or prevent diabetes in over 5000 subjects with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [63]. At three years, subjects who took rosiglitazone, compared with placebo, had a lower incidence of diabetes (HR 0.38, 95% CI 0.33-0.44). This effect was equivalent to the effectiveness of intensive lifestyle intervention in the DPP Trial [36]. There was no difference in mortality, but subjects who took rosiglitazone were more likely to develop heart failure (0.5 percent compared to 0.1 percent for placebo). This finding is particularly significant since participants were free of heart failure at baseline with a mean age of 55 years and BMI of 31 kg/m², and thus represent a population that may be at lower risk for side effects than the general population with IFG or IGT.

These data may reflect the known benefit of [rosiglitazone](#) on glycemic control. The results are not yet available for the effect of a three-year course of rosiglitazone on the incidence of diabetes after drug withdrawal.

Although [rosiglitazone](#) in the DREAM trial was associated with a lower incidence of diabetes than [metformin](#) in the DPP trial, we do not recommend rosiglitazone for diabetes prevention because of adverse effects (fluid retention, weight gain, heart failure, MI) and higher cost. (See "[Thiazolidinediones in the treatment of diabetes mellitus](#)", section on Cardiovascular events).

Pioglitazone — The [Pioglitazone](#) in Prevention of Diabetes (PIPOD) study [64] is similar in concept to the TRIPOD study, and the Actos Now for Prevention of Diabetes (ACT-NOW) is looking at the ability of pioglitazone to prevent or delay diabetes in 600 subjects with IGT and one or more components of the metabolic syndrome. In the interim, we do not suggest using pioglitazone for diabetes prevention.

Alpha-glucosidase inhibitors

Acarbose — [Acarbose](#), an alpha-glucosidase inhibitor, may also be effective for the prevention of type 2 diabetes in patients with impaired glucose tolerance [65], but was not effective in preventing fasting hyperglycemia in patients with early diabetes and postprandial hyperglycemia [66].

- In the STOP-NIDDM trial, 1429 patients with impaired glucose tolerance were randomly assigned to acarbose (100 mg three times daily) or placebo for a mean of 3.3 years [65]. Acarbose therapy resulted in a significantly lower risk of diabetes when compared with placebo (relative hazard 0.75, 95% CI 0.63-0.90). However, 19 percent of patients in the acarbose arm withdrew because of gastrointestinal side effects compared to 5 percent in the placebo group.

In the same trial, [acarbose](#) appeared to reduce the risk of a composite cardiovascular disease outcome in patients with impaired glucose tolerance, a finding that requires further confirmation. (See "[Alpha-glucosidase inhibitors and lipase inhibitors for treatment of diabetes mellitus](#)", section on Effects on cardiovascular events).

- In the Early Diabetes Intervention Program (EDIP), 219 participants with increased risk for diabetes but no previous diagnosis were identified as having early diabetes on the basis of an oral glucose tolerance test (2 hour glucose >200 mg/dL [11.1 mmol/l] and FPG <140 mg dL [7.8 mmol/l]) [66]. Acarbose 100 mg three times daily, compared to placebo, did not significantly reduce the rate of progression to fasting hyperglycemia (29 versus 34 percent) over a five-year follow-up, although it did decrease postprandial hyperglycemia.

The authors postulate that beta cell loss may no longer be reversible, once patients progress from IGT to early diabetes, as defined by the glucose tolerance test.

Although [acarbose](#) was effective in preventing diabetes in individuals with IGT, and it is licensed for this indication in several countries, its use is limited by gastrointestinal side effects and long-

term poor compliance.

Voglibose — Voglibose may also be effective for the prevention of type 2 diabetes in patients with impaired glucose tolerance. In one trial, 1780 Japanese patients with impaired glucose tolerance were randomly assigned to voglibose (0.2 mg three times daily) or placebo [67]. All patients were given advice regarding lifestyle modification. Although the trial was initially planned to continue for five years, an Independent Data Monitoring Committee terminated the study early (mean duration of treatment 48 weeks). In the final analysis, a smaller proportion of patients treated with voglibose progressed to type 2 diabetes (5.6 versus 12 percent in the placebo group, HR 0.59, 98% CI 0.43-0.82). Gastrointestinal adverse effects (flatulence, abdominal distension, diarrhea, constipation) occurred more commonly in the voglibose group.

The early termination of the study may overestimate the prevention benefit of voglibose and precludes any analysis of long-term compliance or benefit. Until additional data are available, we do not recommend voglibose for the prevention of diabetes.

Orlistat — In a four-year randomized trial of [Orlistat](#) for the treatment of obesity, progression to type 2 diabetes was reduced compared with placebo (incidence rate 6.2 versus 9.0 percent) [68]. Exploratory analysis revealed that the preventive effect was explained by the decreased progression to diabetes in the patients with IGT at baseline. The dropout rate was high, and 91 percent of patients in the orlistat group had gastrointestinal side effects. A pooled analysis of three randomized trials reported that orlistat decreased progression to diabetes in subjects with IGT at baseline compared with placebo (3 versus 7.6 percent) [69].

The use of [orlistat](#) for the prevention of diabetes is limited by gastrointestinal side effects and the absence of long-term durability in maintaining weight loss.

Inhibition of angiotensin II — A number of major trials of patients at high risk for cardiovascular disease (HOPE), hypertension with increased risk (ALLHAT), hypertension with ECG evidence of left ventricular hypertrophy (LIFE), and heart failure (CHARM and SOLVD) found that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) significantly reduce the likelihood of new onset type 2 diabetes compared to placebo or other antihypertensive drugs [70-75].

Data from these trials on the incidence of diabetes in the treatment group compared to placebo or other antihypertensive drugs include

- 3.6 versus 5.4 percent with placebo in the HOPE trial [70]
- 6.0 versus 7.4 percent with placebo in the CHARM trials [71]
- 8.1 versus 9.8 percent with [amlodipine](#) and 11.6 percent with low-dose [chlorthalidone](#) (which may be diabetogenic) in the ALLHAT trial [72]
- 6 versus 8 percent with [atenolol](#) in the LIFE trial [73]

In a pooled analysis of 12 randomized controlled trials, ACE inhibitors and ARBs significantly lowered the incidence of newly diagnosed diabetes by 25 percent (14.3 versus 17.4 cases per 1000 patient years, relative risk 0.75, 95% CI 0.69 to 0.82) [76]. The effect was similar with ACE

inhibitors and ARBs. A second meta-analysis of 11 randomized trials also found that the risk of type 2 diabetes for patients with hypertension, coronary disease, or heart failure treated with ACE inhibitors or ARBs was significantly reduced (odds ratio 0.78, 95% CI 0.73 to 0.831) [77]. A third meta-analysis reported similar findings [78].

The above trials were conducted in patients with hypertension, cardiovascular disease, or increased risk for cardiovascular disease, and reduction in diabetes was not a primary endpoint. A subsequent trial, the Diabetes Reduction Assessment with [Ramipril](#) and [Rosiglitazone](#) Medication (DREAM) trial, was designed to evaluate the effect of ramipril on diabetes as the primary outcome in 5269 patients with baseline impaired fasting glucose or impaired glucose tolerance [79]. Ramipril (15 mg per day for a median of three years) did not significantly decrease the incidence of diabetes (17.1 versus 18.5 percent in the placebo group, HR 0.91, 95% CI 0.81 to 1.03). Treatment with ramipril did result in slightly lower plasma glucose levels two hours after a glucose load, but did not improve fasting glucose.

The discrepancy in findings between the DREAM trial and previous trials may relate to ascertainment bias affecting earlier trials, in which participants were not routinely assessed for diabetes at baseline or endpoint. Consistent with this hypothesis are the results of the [Telmisartan](#) to Prevent Recurrent Stroke and Cardiovascular Events trial, in which over 20,000 patients with recent ischemic stroke were randomly assigned to receive telmisartan or placebo [80]. New onset diabetes was a preplanned secondary outcome, and the prevalence of diabetes at baseline was 28 percent. After 2.5 years, there was no difference in the occurrence of newly diagnosed diabetes (1.7 and 2.1 percent) in the telmisartan and placebo groups, respectively (HR 0.82, 95% CI 0.65-1.04).

However, in comparison to other antihypertensive agents, ACE inhibitors and ARBs are less frequently associated with incident diabetes. A meta-analysis of 22 trials (including the DREAM trial), which randomly assigned 143,153 patients who did not have diabetes to an antihypertensive agent, found that ARB and ACE inhibitors were associated with the lowest incidence of diabetes (odds ratio 0.84 [95% CI 0.70 to 1.00] and 0.90 [95% CI 0.78 to 1.04], respectively), followed by calcium channel blockers, placebo, beta blockers, and diuretics [81,82]. A potentially important limitation of this meta-analysis is that it only included trials that reported the number of new cases of diabetes. Trials that did not report this outcome may have done so because there was no difference between the two groups.

In summary, the available data are not conclusive on the possible reduction in new onset diabetes in patients treated with an ACE inhibitor or ARB. Possible mechanisms for an interaction between inhibition of angiotensin II production or activity and glucose metabolism include increased insulin sensitivity and a protective effect on the pancreas via increased blood flow to the pancreas [76,83,84]. Increased insulin sensitivity could be mediated by increased skeletal muscle blood flow, changes in insulin-signaling pathways, or enhanced differentiation of pre-adipocytes into mature adipocytes, which increases the ability of fat cells to store fat and reduces insulin resistance [76,85].

Estrogen therapy — The Heart and Estrogen/progestin Replacement Study (HERS) was a secondary prevention trial in postmenopausal women with established coronary heart disease (CHD) in which the effect of combined estrogen and progestin therapy ([conjugated estrogens](#)

0.625 mg with medroxyprogesterone 2.5 mg daily) or placebo on recurrent CHD events was compared. (See "[Postmenopausal hormone therapy and cardiovascular risk](#)").

At baseline, 734 of 2783 women had diabetes; the remaining 2029 women (who were normoglycemic or had impaired glucose tolerance) were evaluated in a post hoc analysis for the development of type 2 diabetes over an average of 4.1 years [86]. The cumulative incidence of type 2 diabetes was 6.2 percent in the estrogen and progestin group, as compared with 9.5 percent in the placebo group (RH 0.6; 95% CI 0.5 to 0.9).

Similar results were reported in the Women's Health Initiative combined estrogen-progestin trial [87]. After a mean follow-up of 5.6 years, the cumulative incidence of treated diabetes was 3.5 percent in the hormone group and 4.2 percent in the placebo group (HR 0.79, 95% CI 0.7 to 0.9). There was little change in the hazard ratio after adjustment for changes in BMI and waist circumference.

Thus, combined HRT may reduce the risk of type 2 diabetes mellitus. However, this effect is insufficient to recommend HRT as a diabetes prevention strategy in women. (See "[Postmenopausal hormone therapy: Benefits and risks](#)" and see "[Postmenopausal hormone therapy and cardiovascular risk](#)").

ADA GUIDELINES — The goals of intervention in individuals with IGT or IFG include the prevention of diabetes and the associated increased risk of cardiovascular disease. Clinical trials have demonstrated the beneficial effect of lifestyle modification for prevention of diabetes and CVD risk factors (see "[Weight loss/lifestyle intervention](#)" above). The ADA recommends lifestyle modification as the primary intervention in subjects with IGT or IFG [2]. Specific goals include

- Modest weight loss (5 to 10 percent of body weight)
- Moderate-intensity exercise (30 minutes daily)
- Smoking cessation

Pharmacologic agents have also demonstrated some ability to prevent or delay diabetes, whereas the impact on CVD risk factors is less clear and varies with the individual drug. In addition, the long-term effects on cardiovascular events are unknown. Furthermore, the long-term benefits and cost-effectiveness of early pharmacologic treatment versus withholding treatment until diabetes develops are unproven [58].

Because of its effectiveness, low cost, and long-term safety, the ADA recommends consideration of [metformin](#) for prevention of diabetes only in individuals with both IFG and IGT, who are less than 60 years of age and have a BMI ≥ 35 kg/m² or who have additional risk factors ([show table 2](#)) [88].

- Individuals being considered for metformin should have confirmed IFG and IGT (ie, measurements of both a fasting plasma glucose [FPG] and a two-hour OGTT are required to demonstrate the presence of the combined abnormality in glucose homeostasis)
- Patients treated with metformin require monitoring, including twice yearly A1C

assessments

- The ADA recommends screening for IFG/IGT in individuals at high risk for diabetes ([See "Screening for diabetes mellitus"](#), section on Screening recommendations by expert groups)

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. ([See "Patient information: Diabetes mellitus type 2: Overview"](#)). We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS — Subjects with IFG or IGT are at increased risk for macrovascular disease (such as coronary heart disease). Subjects with both IFG and IGT are at even greater risk. As a result, we recommend the following evaluation as part of the routine examination of the subjects. The aim is to identify those who are at relatively high risk for type 2 diabetes and who may have other risk factors for cardiovascular disease ([show table 2](#)):

- Take a family history for type 2 diabetes, hypertension, and hyperlipidemia
- If the subject is obese, estimate whether the excess adipose tissue is in the upper body distribution
- Determine birth weight, if known
- Measure the blood pressure, fasting or random blood glucose, A1C, and fasting serum triglyceride and cholesterol
- Perform two-hour OGTT in individuals with IFG who are less than 60 years of age and have BMI ≥ 35 kg/m²

We recommend counseling all patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on the benefits of weight loss and increasing physical activity. Regular reinforcement of these benefits is important for successful compliance. The subjects should also be encouraged to stop smoking [[88](#)].

Subjects who are at high risk should be followed closely, with repeat examination and measurements of fasting blood glucose and serum lipids on an annual basis [[89,90](#)].

[Metformin](#) therapy can be considered in individuals with both IFG and IGT who have other risk factors for diabetes ([show table 2](#)).

Patients treated with [metformin](#) require monitoring, including twice yearly A1C assessments. ([See "ADA guidelines" above](#)).

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GRAPHICS

Diagnostic thresholds for diabetes and lesser-degrees of impaired glucose regulation

Category	Test	
	FPG	2-h PG
Normal	<100 mg/dL (<5.6 mmol/L)	<140 mg/dL (<7.8 mmol/L)
IFG	100-125 mg/dL (5.6-6.9 mmol/L)	-
IGT	-	140-199 mg/dL (7.8-11.0 mmol/L)
Diabetes*	≥ 126 mg/dL (≥ 7.0 mmol/L)	≥ 200 mg/dL (≥ 11.1 mmol/L)

When both tests are performed. IFG or IGT should be diagnosed only if diabetes is not diagnosed by the other test.

* A diagnosis of diabetes needs to be confirmed on a separate day.

IFG: Impaired fasting glucose

IGT: Impaired glucose tolerance

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Committee on the Diagnosis and Classification of Diabetes Mellitus.

Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care

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Treatment recommendation for individuals with IFG, IGT, or both

Population	Treatment
IFG or IGT	Lifestyle modification (ie, 5-10 percent weight loss and moderate intensity physical activity ~30 min/day)
Individuals with IFG and IGT and any of the following: <60 years of age BMI ≥ 35 kg/m ² Family history of diabetes in first degree relatives Elevated triglycerides Reduced HDL cholesterol Hypertension AIC >6.0 percent	Lifestyle modification (as above) and/or metformin*

* Metformin 850 mg twice per day.

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