

Identification and Treatment of Prediabetes to Prevent Progression to Type 2 Diabetes

VIVIAN A. FONSECA, MD

Professor of Medicine and Pharmacology
Tullis Tulane Alumni Chair in Diabetes
Chief, Section of Endocrinology
Tulane University Health Sciences Center
New Orleans, Louisiana

Overt type 2 diabetes is usually preceded by a condition known as prediabetes, which is characterized by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Both IFG and IGT exhibit elevated glucose levels that are not sufficient to be classified as diabetes but that represent the development of insulin resistance. Achieving glycemic control in patients with prediabetes through lifestyle and pharmacologic interventions can effectively prevent or delay the development of diabetes and its associated complications. The first step, however, is to identify patients at risk. Although patients can be identified with an oral glucose tolerance test (OGTT) or a fasting plasma glucose (FPG) screening, a normal FPG does not preclude an elevated OGTT and, therefore, the presence of prediabetes. For patients who progress to type 2 diabetes, intensive therapy aimed at reducing and maintaining glycosylated hemoglobin (A1C) levels <7% has been shown to reduce the risk of complications. An A1C level $\geq 7\%$ should signal the need to initiate or change therapy to achieve glycemic goals. (*Clinical Cornerstone*. 2007;8[2]:10–20) Copyright © 2007 Excerpta Medica, Inc.

Type 2 diabetes has become a significant public health concern, with an estimated total prevalence of 20.8 million Americans, or 7% of the population, in 2005, including 1.5 million newly diagnosed cases in people aged ≥ 20 years.¹ Prevalence of the disease is higher among minority populations, including non-Hispanic blacks, Hispanic/Latino Americans, Asian Americans, American Indians/Alaska Natives, and Native Hawaiian/Pacific Islanders, than among non-Hispanic whites, and it is being diagnosed more frequently in children and adolescents.¹ Type 2 diabetes is associated with significant morbidity, including an increased risk of heart disease and stroke, hypertension, retinopathy and blindness, end-stage renal disease, and neuropathy leading to amputations.¹ About 65% of deaths among people with diabetes can be attributed to heart disease and stroke, and the risk of stroke and cardiovascular-related death is about 2 to 4 times higher than among people without diabetes.¹ Diabetes is the leading cause of kidney failure and of new cases of blindness among adults aged 20 to 74 years.¹ The risk of death for people with diabetes is also double that for people without the condition.¹

The total cost associated with diabetes in 2002 was estimated to be \$132 billion, with direct costs (ie, the cost of medical care and services) of \$92 billion.¹ Costs associated with chronic complications attributable to diabetes totaled \$24.6 billion.² Diabetes and its complications account for a substantial proportion of costs to the health care system. Per capita medical expenditures totaled \$13,243 for patients with diabetes compared with \$2560 for those without diabetes.² These cost estimates suggest that interventions designed to prevent diabetes can result in a significant cost savings for the health care system as a whole.

Type 2 diabetes is a progressive disease of insulin resistance and defects in insulin secretion due to loss of β -cell function. At the time of diagnosis, only about 50% of β -cell function remains, underscoring the progressive nature of the disease and the importance of early diagnosis and prevention.³ Overt type 2 diabetes is usually preceded by a condition known as *prediabetes*, which is characterized by glucose levels that are higher than normal but not high enough to be classified as type 2 diabetes.¹

There is now a large body of evidence to show that achieving glycemic control in patients with prediabetes through lifestyle and pharmacologic interventions can effectively prevent or delay the development of overt diabetes and its associated complications. Primary prevention of diabetes through lifestyle and pharmacologic interventions (eg, metformin) has also been shown to be cost-effective.^{4,5} This paper discusses the identification and treatment of prediabetes to prevent the development of type 2 diabetes in at-risk patients. The results of several large diabetes prevention trials will also be reviewed.

PREDIABETES

Prediabetes is a condition characterized by impaired glucose metabolism, including the conditions of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Both IFG and IGT result in elevated levels of glucose that are not sufficient to be classified as diabetes (**Table I**)⁶ but that represent the development of insulin resistance, the first step in the progression to type 2 diabetes. IFG is identified by a fasting plasma glucose (FPG) measurement between 100 and 125 mg/dL. IGT is identified by an oral glucose tolerance test (OGTT) in which the 2-hour postprandial or postload measurement is between 140 and 199 mg/dL.⁶

KEY POINT

Prediabetes is characterized by impaired glucose metabolism, including impaired fasting glucose and impaired glucose tolerance.

Insulin resistance in various tissues of the body, including liver, adipose, and muscle, is the primary metabolic abnormality in patients with prediabetes. Prediabetes begins with an accumulation of excess free fatty acids in adipose tissue, as well as nonadipose tissue such as liver, muscle, and pancreas (ie, visceral fat accumulation). The deposition of visceral fat induces the release of pro-inflammatory adipocytokines such as tumor necrosis factor- α , interleukin-6, leptin, and macrophage migration inhibitor factor, which in turn leads to decreased insulin sensitivity.⁷

Prediabetes affects about 41 to 54 million individuals between 40 and 74 years of age in the United States and significantly increases the risk of type 2 diabetes, heart attack, and stroke.¹ However, progression to diabetes is not inevitable. Data from large randomized clinical trials indicate that appropriate lifestyle modifications and pharmacologic interventions in individuals with IFG or IGT can delay or even prevent the onset of type 2 diabetes.

KEY POINT

Appropriate lifestyle modifications and pharmacologic interventions in individuals with IFG or IGT can delay or even prevent the onset of type 2 diabetes.

LIFESTYLE INTERVENTIONS TO PREVENT DIABETES

Several trials have demonstrated the efficacy of diet and exercise regimens in reducing the incidence of diabetes among individuals with IFG or IGT (**Table II**).^{8–10} The Da Qing IGT and Diabetes Study⁸ randomized 577 patients with IGT to a control group or to 1 of 3 active treatment groups: diet only, exercise only, or diet and exercise. At the 6-year follow-up, the cumulative incidence of diabetes was 67.7% in the control group versus 43.8% in the diet group, 41.1% in the exercise group, and 46.0% in the diet and exercise group ($P < 0.05$ for all comparisons). The diet

TABLE I. DEFINITIONS: PREDIABETES AND DIABETES.⁶

Prediabetes

Impaired fasting glucose:

Fasting plasma glucose* 100–125 mg/dL (5.6–6.9 mmol/L)

Impaired glucose tolerance:

2-Hour plasma glucose† 140–199 mg/dL (7.8–11.0 mmol/L)

Diabetes

Fasting plasma glucose:

≥ 126 mg/dL (≥ 7.0 mmol/L)

2-Hour plasma glucose:

≥ 200 mg/dL (≥ 11.0 mmol/L)

*Fasting = no caloric intake for ≥ 8 hours.

†Measured by oral glucose tolerance test using a 75-g glucose load.

TABLE II. LIFESTYLE INTERVENTIONS TO PREVENT DIABETES IN PATIENTS WITH PREDIABETES.

Study	Population	Study Protocol	Effect on Diabetes Incidence
Da Qing IGT and Diabetes Study ⁸	Patients with IGT (n = 577)	Diet; exercise; or diet plus exercise	Reductions: 31%, 46%, and 42%, respectively
Diabetes Prevention Program ⁹	Patients with IGT (n = 3234)	Intensive lifestyle intervention; or standard lifestyle intervention plus placebo or metformin	Reductions: intensive lifestyle 58% vs placebo, 39% vs metformin
Finnish Diabetes Prevention Study ¹⁰	Overweight patients with IGT (n = 522)	Lifestyle intervention; or control group	Reduction: lifestyle intervention 58% vs control group

IGT = impaired glucose tolerance.

only, exercise only, and diet and exercise interventions were associated with a 31% ($P < 0.03$), 46% ($P < 0.001$), and 42% ($P < 0.005$) reduction in the risk of developing diabetes, respectively. Interestingly, the greatest reduction in the risk of developing diabetes occurred in the exercise group, underscoring the importance of physical activity in any diabetes prevention program.

These results were supported by findings from the Diabetes Prevention Program (DPP).⁹ After a mean follow-up of 2.8 years, the incidence of diabetes among patients with IGT who were randomized to intensive lifestyle modification was reduced by 58% compared with patients randomized to standard lifestyle modification plus placebo, and by 39% compared with standard lifestyle modification plus metformin 850 mg BID. The goal of the intensive lifestyle intervention was to achieve and maintain a weight reduction of $\geq 7\%$ of body weight via a healthy low-calorie, low-fat ($< 25\%$ of calories) diet and physical activity of moderate intensity (≥ 150 min/wk). Patients initially received 16 individualized sessions on lifestyle modification in addition to subsequent individual and group sessions. Standard lifestyle modification included written recommendations and an annual 20- to 30-minute individual session emphasizing the importance of a healthy lifestyle.

The Finnish Diabetes Prevention Study produced nearly identical results.¹⁰ In this study, 522 overweight patients with IGT were randomized either to a control group or to lifestyle intervention, which consisted of individualized counseling designed to help patients reduce weight and fat intake and increase physical activity and fiber intake. The mean weight reduction was 4.2 kg from baseline to year 1 and 3.5 kg from year 1 to year 2. At a mean follow-up of 3.2 years, the incidence of diabetes was reduced by 58% in the intervention group compared with the control group

($P < 0.001$). Interestingly, these lifestyle changes were maintained and the diabetes risk reduction sustained, even after a mean follow-up of 7 years, which was well after discontinuation of the intervention. These results suggest that initiation of lifestyle changes can produce sustained changes in behavior and reductions in the risk of diabetes.

Lifestyle interventions also have been shown to be cost-effective. In one study,⁴ lifestyle modification was more cost-effective than metformin monotherapy. In another study,⁵ community-based lifestyle interventions were found to be cost-effective in low- and moderate-risk patients, but only intensive lifestyle interventions implemented in a health care setting were cost-effective in high-risk patients.

PHARMACOLOGIC INTERVENTIONS FOR THE PREVENTION OF DIABETES

Several oral agents, including metformin, the thiazolidinediones (TZDs), acarbose, and orlistat, have been evaluated for the prevention of diabetes and cardiovascular disease in patients with IFG or IGT (Table III).^{9,11-16}

Metformin

In the DPP discussed earlier,⁹ treatment with metformin resulted in a 31% reduction in the risk of diabetes, but it was significantly less effective than the intensive lifestyle intervention. Notable in this trial was the fact that, in the group receiving metformin, it was adherence to pharmacologic treatment that was associated with the reduction in diabetes incidence. Those who adhered to the metformin treatment regimen had a 24.8% reduction in risk for developing diabetes compared with those who did not.¹⁷ These results underscore the need for strategies designed to improve and maintain adherence during long-term antidiabetic therapy.

TABLE III. ORAL AGENTS TO PREVENT DIABETES OR CARDIOVASCULAR (CV) EVENTS IN PATIENTS WITH PREDIABETES.

Study	Population	Intervention	Effect
DPP ⁹	Patients with IGT (n = 3234)	Metformin 850 mg BID or placebo	Reduced risk of diabetes: 31% with metformin vs placebo
TRIPOD ¹¹	Hispanic women with gestational diabetes (n = 266)	Troglitazone or placebo	Reduced incidence of diabetes: 55% with troglitazone vs placebo
DREAM ^{12,13}	Patients with IFG or IGT (n = 5269)	Rosiglitazone 8 mg/d or placebo, plus ramipril ≤15 mg/d or placebo	Reduced risk of diabetes: 60% with rosiglitazone; 9% with ramipril
STOP-NIDDM ¹⁴	Patients with IGT (n = 1429)	Acarbose 100 mg TID or placebo	Reduced relative risk of diabetes: 25% with acarbose vs placebo Reduced risk of CV events: 49% with acarbose vs placebo
Chinese Acarbose Study ¹⁵	Chinese patients with IGT (n = 261)	Acarbose 50 mg TID or placebo	Reduced conversion to diabetes: 7 vs 12 with acarbose vs placebo
XENDOS ¹⁶	Obese patients with or without IGT (n = 3305)	Orlistat 120 mg TID or placebo, plus lifestyle intervention	Reduced risk of diabetes: 37.3% with orlistat for all patients, 45% for patients with IGT vs placebo

DPP = Diabetes Prevention Program; IGT = impaired glucose tolerance; TRIPOD = Troglitazone In the Prevention Of Diabetes; DREAM = Diabetes REduction Assessment with ramipril and rosiglitazone Medication; IFG = impaired fasting glucose; STOP-NIDDM = Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus; XENDOS = XENical in the prevention of Diabetes in Obese Subjects.

Thiazolidinediones

The DPP trial originally included a troglitazone treatment arm that was abruptly discontinued after a fatal case of liver failure occurred in a study participant. Troglitazone was subsequently withdrawn from the market. An analysis¹⁸ of the patients in the troglitazone arm of the trial (mean duration, 10 months) who continued to undergo follow-up showed that troglitazone significantly reduced the incidence of diabetes compared with metformin ($P < 0.02$) and placebo ($P < 0.001$); however, this reduction came at the expense of significantly greater weight gain (mean, 4 kg) compared with the other 3 treatment groups. Although treatment with troglitazone resulted in a 75% reduction in the incidence of diabetes versus placebo during its use, after discontinuation of treatment, patients who had received troglitazone had a diabetes incidence rate identical to that of the patients in the placebo group.

The TRIPOD (Troglitazone In the Prevention Of Diabetes) study evaluated the effect of treating insulin resistance with troglitazone on the incidence of diabetes in Hispanic women with gestational diabetes, a high-risk patient group.¹¹ During a mean follow-up of 30 months, troglitazone reduced the incidence of diabetes by 55%. In contrast to the results of DPP, however, the TRIPOD

study found that the protective effect of troglitazone against the development of diabetes was preserved, even 8 months after the medication was discontinued. When troglitazone was withdrawn from the market in 2000, patients who had completed the TRIPOD study were enrolled in the PIPOD (Pioglitazone In the Prevention Of Diabetes) study,¹⁹ which evaluated the effect of pioglitazone on diabetes risk. In this study, pioglitazone not only reduced the risk of developing diabetes but also stopped the decline in β -cell function (as measured by IV glucose tolerance tests) that occurred in patients randomized to receive placebo in the original TRIPOD study. The consistent results of the TRIPOD and PIPOD studies suggest that the improvements were a result of a TZD class effect.

The class effect of TZDs on the risk of diabetes was confirmed recently in the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial,¹² which evaluated the efficacy of ramipril and rosiglitazone in preventing new cases of diabetes in 5269 patients with IGT, IFG, or both. Patients were randomized to treatment with ramipril (≤ 15 mg/day) or placebo and, concurrently, to rosiglitazone (8 mg/day) or placebo, according to a 2×2 factorial design. Patients also received brief counseling about the importance of healthy diet and

lifestyle habits in preventing diabetes. Mean follow-up was 3.0 years. Treatment with rosiglitazone was found to reduce the risk of diabetes or death by 60% in patients with markers of prediabetes, although the incidences of edema and heart failure were significantly higher in the rosiglitazone group than in the placebo group.¹² Ramipril, like rosiglitazone, increased the likelihood of regression of IGT or IFG to normoglycemia; however, treatment with ramipril did not significantly reduce the risk of death or diabetes compared with placebo in patients with prediabetes, and mean FPG at the end of the study was not significantly different in the ramipril group compared with the placebo group.¹³

Pioglitazone and rosiglitazone do not appear to have the same hepatotoxic effect as troglitazone; however, TZDs have been shown to increase total cholesterol and low-density lipoprotein cholesterol levels, as well as body weight.²⁰ In addition, a recent meta-analysis showed a significant increase in the risk of myocardial infarction (MI) and a borderline significant risk of death from cardiovascular causes with rosiglitazone.²¹ Whether this is a class effect is not yet known; however, these risks should be considered when weighing the appropriateness of treatment with a TZD.

Acarbose

In the STOP-NIDDM (Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus) trial,¹⁴ 1429 patients with IGT were randomized to receive placebo or 100 mg acarbose TID. The discontinuation rate was particularly high in this trial, with 31% of patients randomized to acarbose and 19% of patients randomized to placebo discontinuing treatment early. Nevertheless, at follow-up (mean, 3.3 years), treatment with acarbose resulted in a 25% relative risk reduction in the development of diabetes, a 34% reduction in the development of hypertension, and a 49% reduction in the risk of cardiovascular events, particularly MI. In this trial, treatment with acarbose not only reduced the incidence of diabetes but also the risk of cardiovascular disease (CVD) in prediabetic patients.

The multicenter, double-blind, placebo-controlled study by Pan and colleagues¹⁵ contributes further evidence of the beneficial effects of acarbose. A total of 261 Chinese individuals with IGT determined using a 75-g OGTT was enrolled in the study. Participants were randomized to placebo or acarbose 50 mg QD for 1 week, BID for 2 weeks, and TID for the remaining weeks of the

16-week study. The intent-to-treat analysis showed significantly greater reductions in 2-hour postprandial glucose concentrations (12%), serum insulin concentrations (25.5%), and triglyceride concentrations (5.6%) versus placebo, and weight loss was significantly greater (4.3%). In addition, fewer participants converted to type 2 diabetes in the acarbose group compared with those in the placebo group (7 vs 12).

Orlistat

The XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study¹⁶ hypothesized that the addition of orlistat, a weight-reducing agent, would enhance the diabetes preventive effect of lifestyle intervention in a high-risk group of obese patients with and without prediabetes. After 4 years of treatment, the cumulative incidence of diabetes in the group receiving orlistat TID in addition to lifestyle intervention was 6.2% versus 9.0% in patients receiving lifestyle intervention and placebo, a relative risk reduction of 37.3%. Mean weight loss after 4 years was 5.8 kg in the orlistat group versus 3.0 kg in the control group. The difference in diabetes incidence between the orlistat and control groups was significant only among patients with IGT. In patients with IGT treated with orlistat, the incidence of diabetes was reduced by 45% compared with those receiving placebo (18.8% vs 28.8%; $P = 0.017$).

STRATEGIES FOR TARGETING PREDIABETES

Recent analyses have outlined strategies for targeting prediabetes to prevent progression to type 2 diabetes and its associated complications. The first step is to identify patients at risk—these include obese patients who are insulin resistant, obese patients who are metabolically healthy, and normal weight patients who are metabolically obese.⁷ Obese individuals who are metabolically healthy have lower levels of visceral fat, fasting insulin, plasma triglycerides, and highly sensitive C-reactive protein, and higher levels of high-density lipoprotein cholesterol. Normal weight individuals who are metabolically obese have higher levels of visceral fat and are insulin resistant (measured by fasting insulin, fasting glucose, and intact proinsulin). Patients at risk for diabetes can be identified with an OGTT or by FPG value; yet an individual can have a normal FPG value but an elevated OGTT value and therefore be prediabetic.⁷

KEY POINT

The first step in preventing type 2 diabetes and its associated complications is to identify obese patients who are insulin resistant, obese patients who are metabolically healthy, and normal weight patients who are metabolically obese.

Lifestyle interventions aimed at reducing energy intake and increasing physical activity have a direct impact on insulin resistance and the incidence of diabetes, as discussed above. A gradual decrease in caloric intake of ~500 to 1000 kcal/d, along with moderately intense physical activity (150 min/wk), can lead to progressive weight loss. Reducing the intake of saturated fat, trans fatty acids, and cholesterol improves lipid profiles and insulin sensitivity.⁷ The National Cholesterol Education Program recommends that daily intake of total fat be no more than 25% to 35% of total calories and that daily intake of saturated fat be <7% of total calories.⁷

KEY POINT

Lifestyle interventions aimed at reducing energy intake and increasing physical activity have a direct impact on insulin resistance and the incidence of diabetes.

A follow-up analysis of the DPP evaluated the lifestyle intervention arm to determine the relative contributions of weight loss, changes in diet, and physical activity to the reduced incidence of diabetes observed in the study.²² In this analysis of 1079 patients, weight loss was found to be the strongest predictor of reduced diabetes incidence. For every 1 kg of weight lost there was a 16% reduction in the risk of developing diabetes. Physical activity was found to help sustain the weight loss. Results of the DPP showed that the incidence of diabetes was 44% lower among the patients who achieved the intended weight loss and physical activity goals.²²

Physical activity may have benefits independent of weight loss as well. Exercise and moderately intense physical activity increase the uptake of glucose into muscle tissue and reduce hepatic glucose output. Therefore, physical activity may directly improve insulin resistance and reduce plasma glucose concentrations.

PREVENTION OF DIABETES COMPLICATIONS

As discussed above, the progression from prediabetes to overt type 2 diabetes can be prevented with intensive lifestyle interventions that modify diet and increase physical activity, and with the addition of pharmacologic agents such as metformin, acarbose, or a TZD, as needed. However, for patients who progress to overt type 2 diabetes, a regimen that quickly achieves and maintains glycemic goals is recommended.

KEY POINT

For patients who progress to overt type 2 diabetes, a regimen that quickly achieves and maintains glycemic goals is recommended.

The benefit of early intensive treatment to achieve glycemic control has been demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS).²³ Compared with conventional therapy (dietary control), patients with newly diagnosed diabetes who received intensive therapy with a sulfonylurea or insulin with the goal of achieving an FPG <108 mg/dL achieved risk reductions of 12% for any diabetes-related end point, 10% for any diabetes-related death, and 6% for all-cause mortality. Over 10 years, mean glycosylated hemoglobin (A1C) values were 7.0% in the intensive-therapy group versus 7.9% in the conventional-therapy group.

Similarly, intensive treatment with metformin, again to achieve an FPG <108 mg/dL, was found to be significantly more effective than conventional therapy in reducing diabetes-related complications and mortality.²⁴ Compared with patients in the conventional-therapy group, those randomized to intensive metformin therapy achieved risk reductions of 32% for any diabetes-related end point, 42% for diabetes-related death, and 36% for

all-cause mortality. Metformin also had a significantly greater effect than insulin, chlorpropamide, or glibenclamide with respect to any diabetes-related end point, all-cause mortality, and stroke.

Intensive therapy aimed at reducing and maintaining A1C levels <7% has also been shown to reduce the risk of diabetic complications, such as retinopathy, nephropathy, and neuropathy, by 35% to 90% in patients with type 1 diabetes.²⁵

A recent consensus statement issued by the American Diabetes Association and the European Association for the Study of Diabetes outlines an approach to the management of hyperglycemia in adults with type 2 diabetes.²⁶ The general goal is to maintain A1C levels <7% or as close to normal (<6%) as possible without significant hypoglycemia. Importantly, an A1C level $\geq 7\%$ should signal the need to initiate or change therapy to achieve glycemic goals. However, decisions to initiate or change therapy should take into account other factors, including a patient's risk of hypoglycemia and any comorbidities.

The initial recommended treatment for patients with type 2 diabetes is the combination of lifestyle intervention (ie, decreased calorie consumption and increased physical activity) to achieve and maintain weight loss and pharmacologic treatment with metformin.²⁶ Diet regimens should also aim to improve blood pressure levels (eg, by limiting salt intake) and lipid profiles (eg, by reducing cholesterol and saturated fat intake). Metformin monotherapy typically reduces A1C levels by $\sim 1.5\%$, and it is not associated with hypoglycemia, even in individuals with prediabetic hyperglycemia. Metformin has the added nonglycemic benefit of inducing a small amount of weight loss. Metformin should be titrated to maximally effective and tolerated doses over 1 to 2 months.

If these interventions fail to achieve A1C levels <7% after 2 to 3 months, the patient's treatment regimen should be intensified by adding either another class of oral antidiabetic agent (eg, a sulfonylurea or a TZD) or by adding insulin.²⁶ Sulfonylureas have the advantage of lower associated costs, while TZDs, unlike sulfonylureas and insulin, are not associated with hypoglycemia. However, the choice of adjuvant agent should be based on the A1C level achieved after the initial interventions have failed. For example, for patients with A1C levels >8.5%, symptoms of hyperglycemia, or very high FPG levels (>250–300 mg/dL), insulin therapy is recommended, as it is the most effective agent for rapidly lowering

A1C levels.^{6,26} If A1C goals are not met through lifestyle intervention and treatment with metformin and a second agent, therapy should be further intensified. If initial A1C levels are close to goal (ie, <8.0%), initiating or intensifying insulin therapy is usually more effective and less costly than adding a second or third oral agent.²⁶

ONGOING TRIALS

Several trials are currently investigating the potential of various classes of drugs alone or in combination to prevent the progression to diabetes and cardiovascular events. For example, The NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study²⁷ is investigating the progression of type 2 diabetes and CVD and examining the potential of valsartan \pm nateglinide to delay or prevent the development of these diseases. NAVIGATOR is a large prospective, multinational, randomized, double-blind, placebo-controlled, 2×2 factorial design trial being conducted at ~ 800 sites in 39 countries. Of the >43,000 people screened for the study, 22% ($n = 9092$) were found to have undiagnosed type 2 diabetes, and 28% ($n = 11,853$) were found to have unrecognized IGT. Results of this study are expected to be reported in 2008.

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) study²⁸ is investigating whether use of the 24-hour basal insulin analogue, insulin glargine, can reduce the incidence of cardiovascular events such as heart attack and stroke in people with early diabetes or prediabetes who are at high risk for CVD. A total of 10,000 participants from 600 sites in >35 countries is expected. Study participants must have IFG, IGT, or early diabetes, as well as ≥ 1 high-grade cardiovascular risk factor, such as microalbuminuria or left ventricular hypertrophy, or a previous cardiovascular event, such as an MI or stroke. The study is examining the use of glargine versus standard management of blood glucose elevation, and the importance of diet and lifestyle modification will be emphasized to all participants.

Tight control of blood pressure is essential for the prevention of cardiovascular events in high-risk patients. ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)²⁹ is designed to compare the effects of telmisartan, an angiotensin receptor blocker, and ramipril, an angiotensin-converting enzyme inhibitor, on cardiovascular mortality and morbidity in high-risk patients. In this study, high

risk is defined as a history of coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes with target-organ damage. ONTARGET is a randomized, double-blind, parallel-group study of 25,620 patients (age ≥ 55 years) recruited from >700 centers in 40 countries. The primary end point is the composite of cardiovascular mortality, nonfatal stroke, acute MI, and hospitalization for congestive heart failure. Secondary end points are newly diagnosed heart failure, diabetes mellitus, or atrial fibrillation; revascularization; development of dementia or cognitive decline; and neuropathy. Planned duration of follow-up is 5.5 years. Results are expected in 2007.

CONCLUSIONS

Type 2 diabetes and its associated complications represent an enormous burden to the health care system and society as a whole. Several large clinical trials have shown that appropriate lifestyle and pharmacologic interventions aimed at achieving glycemic control can delay or prevent the progression of prediabetes to overt type 2 diabetes and its associated complications.

REFERENCES

- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). National diabetes statistics. Available at: <http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/>. Accessed April 25, 2007.
- American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917–932.
- UK Prospective Diabetes Study Group. UK Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease [published correction appears in *Diabetes*. 1996;45:1655]. *Diabetes*. 1995;44:1249–1258.
- Icks A, Rathmann W, Haastert B, et al, for the KORA Study Group. Clinical and cost-effectiveness of primary prevention of type 2 diabetes in a 'real world' routine healthcare setting: Model based on the KORA Survey 2000. *Diabet Med*. 2007;24:473–480.
- Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, et al. Lifestyle interventions are cost-effective in people with different levels of diabetes risk. Results from a modeling study. *Diabetes Care*. 2007;30:128–134.
- American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care*. 2007;30(Suppl 1):S4–S41.
- Biuso TJ, Butterworth S, Linden A. A conceptual framework for targeting prediabetes with lifestyle, clinical, and behavioral management interventions. *Disease Management*. 2007;10:6–15.
- Pan X-R, Li G-W, Hu Y-H, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerances. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537–544.
- Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
- Lindstrom J, Eriksson JG, Valle TT, et al. Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: Results from a randomized clinical trial. *J Am Soc Nephrol*. 2003;14(Suppl 2):S108–S113.
- Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.
- DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: A randomised controlled trial. *Lancet*. 2006;368:1096–1105.
- DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355:1551–1562.
- Chiasson J-L, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. The STOP-NIDDM trial. *JAMA*. 2003;290:486–494.
- Pan C-Y, Gao U, Chen J-W, et al. Efficacy of acarbose in Chinese subjects with impaired glucose tolerance. *Diabetes Res Clin Pract*. 2003;61:183–190.
- Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study. *Diabetes Care*. 2004;27:155–161.
- Walker EA, Molitch M, Kramer MK, et al. Adherence to preventive medications: Predictors and outcomes in the Diabetes Prevention Program. *Diabetes Care*. 2006;29:1997–2002.
- Ratner RE, for the Diabetes Prevention Program Research Group. An update on the Diabetes Prevention Program. *Endocr Pract*. 2006;12(Suppl 1):20–24.
- Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic β -cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes*. 2006;55:517–522.
- Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med*. 2001;134:61–71.
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:1304–1316.
- Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*. 2006;29:2102–2107.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.

25. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 2002;287:2563–2569.
26. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29:1963–1972.
27. NAVIGATOR data presented at American Heart Association's Scientific Sessions provide new insights about cardiovascular and diabetes risk (November 16, 2005). Available at: <http://www.pharma.us.novartis.com/newsroom/pressReleases/releaseDetail.jsp?PRID=1885>. Accessed July 16, 2007.
28. PRNewswire-First Call (February 17, 2004). Aventis S.A. announces five-year ORIGIN trial to investigate reduction in heart disease risk with Lantus® insulin. Available at: http://www.biospace.com/news_story.aspx?NewsEntityId=15175820. Accessed July 16, 2007.
29. Weber MA. Hypertension treatment and implications of recent cardiovascular outcome trials. *J Hypertens*. 2006; 24(Suppl 2):S37–S44.

Address correspondence to: Vivian A. Fonseca, MD, Professor of Medicine and Pharmacology, Tullis Tulane Alumni Chair in Diabetes, Chief, Section of Endocrinology, Tulane University Health Sciences Center, 1430 Tulane Avenue - SL 53, New Orleans, LA 70112. E-mail: vfonseca@tulane.edu

Dialogue Box

EDITORIAL BOARD

Should clinicians be satisfied with a glycosylated hemoglobin (A1C) of <7% in their patients?

FONSECA

A normal A1C is <6% and that ideally should be the target. However, efforts aimed at reducing it to that value are often limited by the risk for hypoglycemia. Settling for a level of <7% would represent a trade-off between a reduced risk of diabetic complications and the risk of hypoglycemia. The need for balancing these 2 risks is evident in the current American Diabetes Association (ADA) recommendation. If you can get the A1C <6% without unacceptable side effects (ie, hypoglycemia), then that should be the goal. At a minimum, you should strive to get it <7%.

EDITORIAL BOARD

Which of the 2 tests is more sensitive for detecting prediabetes: the fasting glucose or the 2-hour post-load glucose?

FONSECA

In the cohort of patients studied in the Diabetes Prevention Program (DPP) (ie, patients with risk factors for diabetes, such as obesity or a history of gestational diabetes), very few had an isolated impaired fasting glucose (ie, fasting glucose between 100 and 126 mg/dL) with normal glucose tolerance (2-hour postload glucose <140 mg/dL). On the other hand, 25% of patients with impaired glucose tolerance (2-hour postload glucose between 140 and 200 mg/dL) will have a completely normal fasting glucose. Notably, there are a few people, usually older people, with a fasting glucose between 100 and 126 mg/dL and a 2-hour glucose >200 mg/dL and who have diabetes—these are the ones we need to be on the lookout for. Thus, if I have an older patient with a fasting glucose of 115 mg/dL, I often will order a glucose tolerance test to rule out diabetes.

EDITORIAL BOARD

Since neither of these tests appears to be infallible, why not use the A1C as a screen?

FONSECA

There are several reasons why this is not recommended. First, since A1C is the glycated fraction of hemoglobin A, it is inaccurate in patients with hemoglobinopathies, such as sickle cell trait, hemoglobin C, or thalassemia minor. The second reason is cost. Although the actual cost of an A1C test is \$5 to \$8, the cost to the patient is likely to be much higher. Third, the correlation of the A1C assay and its relationship to glucose is very good in the 7% to 9% range but less so at ~6%. Thus, you might have a normal patient with a “true value” of 5.9% and yet the assay might come back 6.1% (which is well within the acceptable limitations of the instrument) and falsely identify the patient as diabetic. Neither the fasting nor the 2-hour glucose tests are perfect, but they are a lot more precise than the A1C in a patient whose A1C hovers at ~6%. Suffice it to say that the methodology for A1C was really not designed with precision at that end of the spectrum in mind when it was developed.

EDITORIAL BOARD

When counseling patients with prediabetes, some clinicians cite a risk of developing diabetes of 30% to 50% over the next 5 to 10 years. Do you agree with this estimate?

FONSECA

That would be a fair starting point, although recognize that the risk is highly variable. Women with a history of gestational diabetes have a rate of conversion to diabetes as high as 8% a year. In the DPP, which included people deemed to be at high risk, the risk was about 30% over the 4 years of the study.

EDITORIAL BOARD

Although the ADA recommends lifestyle interventions in patients with prediabetes, it discourages the use of pharmacologic therapy. What do you think of the strategy of initiating lifestyle interventions and, in those patients who continue to gain weight and whose fasting glucose continues to rise (yet remains <126 mg/dL), starting a drug like metformin?

Dialogue Box

FONSECA

First, let me say that that would be an off-label use of the medication, one not approved by the US Food and Drug Administration (FDA). Second, let me underscore that writing such a prescription without giving lifestyle intervention a fair trial would be a bit of a cop-out. Having said this, I think it is a fairly pragmatic approach and I expect that, in time, there will be sufficient pressure on the FDA to approve a drug like metformin to prevent diabetes because of the economic and health care burden of the disease. In considering this strategy, one should also consider the responsiveness of metformin in different situations. The DPP found that obese people responded better to metformin, as did younger subjects. Thus, the desired response would more likely be achieved in an obese patient <50 years of age than in an older, nonobese patient. If you start metformin in the latter, you may simply end up treating diabetes early as opposed to impacting its natural history in terms of progression. On the other side of the coin, I don't think there is much wrong with treating diabetes early. By preventing somebody from developing the microvascular complications of diabetes, in a way you have prevented diabetes.

EDITORIAL BOARD

What are your thoughts regarding the increased cardiovascular risk seen with rosiglitazone in the recently published Nissen meta-analysis?

FONSECA

I think what it showed was a slight statistically significant increase in relative risk. However, the absolute risk in the population evaluated appeared relatively small. Thus, patients should not really panic, thinking that it is going to cause them to have a heart attack. I think if the risk for cardiovascular complications is very low, as in the subjects with prediabetes studied in the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial, the risk of using rosiglitazone is probably not worth taking. However, in people

with more advanced diabetes in whom it is clearly important to optimize glycemic control, any possible absolute increase in risk due to rosiglitazone would likely be offset by the potential benefit gained by improved glycemic control. In looking at relative risk, one really needs to consider the context and consider relative to what. If the risk appears to be higher when compared with metformin, that would not be surprising. Furthermore, if you are on metformin and it is no longer working, what is the point of saying that your relative risk of a heart attack is lower if you are going to have an increased relative risk of getting kidney disease or retinopathy? With regard to using rosiglitazone, I must say that I found the results of the ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) studies reassuring since these long-term trials found that in a reasonable number of patients, there appeared to be no increased risk.

EDITORIAL BOARD

Do you think there will be a cure for type 2 diabetes in our lifetime?

FONSECA

I hope there will someday be a cure. It has become such a major clinical problem that we need to find a cure. But for now, the important thing is that type 2 diabetes is preventable and prevention is always better than a cure. I have little doubt that much of the diabetes epidemic that we are seeing today is driven by obesity, physical inactivity, and excessive food intake. The challenge before us is to translate the lifestyle changes used in the DPP into the general population. This is going to require, in my opinion, societal change. We need to build our communities and cities in a way that encourages people to walk and to be more physically active. Studies done in Japan have shown that people who walk 20 minutes a day to work get less diabetes than those in the same company who drive to work.