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1. Title Page
   Page i

2. Faculty List
   Page iv

3. Faculty Disclosures
   Page v

4. CME information
   Pages vi-vii

5. Introduction
   Pages S1-S2
   Burton E. Sobel

6. Optimizing Cardiovascular Outcomes in Diabetes Mellitus
   Pages S3-S11
   Burton E. Sobel

7. Diabetes Mellitus and Macrovascular Disease: Mechanisms and Mediators
   Pages S12-S17
   Patrick J. Boyle

8. Rationale for the Use of Insulin Sensitizers to Prevent Cardiovascular Events in Type 2 Diabetes Mellitus
   Pages S18-S25
   Vivian A. Fonseca

9. Prevention of Macrovascular Disease in Patients with Diabetes Mellitus: Opportunities for Intervention
   Pages S26-S32
   Theodore Mazzone

10. CME section
    Pages S35, S37, S39, S40
Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action

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Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action

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Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action

Program Overview

The complex interplay between lipid metabolism, insulin sensitivity, blood pressure, coagulation, inflammation, oxidative stress, obesity, and a host of other factors highlights the need for a multidisciplinary approach to management of cardiovascular risk and macrovascular disease in persons with diabetes mellitus.

During a CME/CE-certified symposium held on November 12, 2006 in Chicago, Illinois, a distinguished panel of experts presented the outcomes of deliberations of a multidisciplinary steering committee that had reviewed the management of macrovascular disease in patients with diabetes. The symposium was a call to action for healthcare professionals involved in the care of patients at risk for cardiovascular events as a consequence of diabetes.

This educational activity explores the association between diabetes and cardiovascular events, including the mechanisms through which disorders of metabolism and the endocrine and cardiovascular systems interact in the patient with diabetes, ultimately leading to macrovascular disease. Data supporting current management options are provided, along with information pertaining to emerging treatment strategies.

Target Audience

This activity has been developed for clinicians, nurses, and pharmacists involved in the care of patients with diabetes mellitus.

Educational Objectives

At the conclusion of this activity participants should be able to:

- Discuss the pathophysiology and impact of macrovascular disease on patients with diabetes
- Summarize the evidence that intervention with insulin sensitizers, particularly pioglitazone, reduces the incidence of cardiovascular events in patients with diabetes
- Describe potential mechanisms by which thiazolidinediones are beneficial in the prevention and treatment of macrovascular disease
- Demonstrate effective cross-disciplinary management of diabetes, including a consideration of macrovascular disease and strategies to improve outcomes

Method of Instruction

Participants should carefully review the entire activity, including the program overview, educational objectives, target audience description, and other material in this CME/CE Information section. After review, read the text, and complete and submit answers to the CME/CE Assessment Test, Registration Form, and Evaluation Form.

Participants must achieve a passing grade of ≥70% to receive credit. Please be sure to complete and return both the Registration Form and the Activity Evaluation Form to receive the appropriate credit.

There is no fee for participation. The estimated time to complete this educational activity is 1.75 hours.

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This activity has been accredited for 1.75 contact...
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ACPE #309-000-07-005-H04

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Introduction

The risk of death from cardiovascular disease is high in patients with diabetes mellitus. Indeed, in the United States, diabetes is the most prevalent risk factor for cardiovascular events. Results of several studies have demonstrated the risk for myocardial infarction (MI) in patients with diabetes to be approximately the same as that for recurrent myocardial infarction (MI) in patients without diabetes. Accordingly, macrovascular complications are the principal reason for a decrease in life expectancy of approximately 8 years in patients with diabetes.

Cardiovascular disease related to diabetes comprises a significant health burden, particularly because the incidences of both obesity and diabetes are increasing. For example, age-adjusted mortality rates decreased by 21% for women and 30% for men in New York City between 1990 and 2000, whereas diabetes-related mortality actually increased by 61% and 52%, respectively. Age-adjusted hospitalization rates for acute MI remained unchanged, principally as a result of an increase in the number of individuals with diabetes (relative risk [RR], 1.54), which offset a decrease in those who did not have diabetes (RR, 0.86).

A number of factors are thought to be important in the pathogenesis of coronary artery disease in patients with diabetes. Hyperglycemia and hyperinsulinemia contribute to endothelial dysfunction. Dyslipidemia is a well known risk factor for coronary atherosclerosis, and lipid abnormalities (high levels of low-density lipoprotein [LDL], low levels of high-density lipoprotein, and high levels of triglycerides) are often present in patients with diabetes. However, in addition, with lipids at any given level, patients with diabetes have more severe coronary artery disease compared with that in patients without diabetes but comparable concentrations of lipids, possibly in part because of increased concentrations of small, dense LDL cholesterol particles. In addition, insulin resistance is associated with several changes to the cardiovascular system, resulting in endothelial dysfunction, a prothrombotic and antifibrinolytic state, and decreased plaque stability.

Although stringent glucose control reduces the incidence of microvascular complications of diabetes, its impact on macrovascular complications is less robust. It is likely, as judged from emerging evidence, that some specific antidiabetic therapeutic interventions, particularly those using agents that increase insulin sensitivity, such as the thiazolidinediones, may have actions beyond glycemic control that can affect the risk and progression of macrovascular disease favorably.

To further explore the association between diabetes and cardiovascular events, a multidisciplinary steering committee was convened by Strategic Consultants International and CME Consultants as part of an educational grant from Takeda Pharmaceuticals North America. This group considered the mechanisms through which disorders of metabolism and the endocrine and cardiovascular systems interact in the patient with diabetes and sought to identify opportunities for the optimal management of cardiovascular risk. This steering committee developed a series of statements summarizing their findings, which are presented in this supplement to The American Journal of Medicine.

The first article, by Dr. Burton E. Sobel, reviews significant aspects of macrovascular disease in patients with diabetes, focusing in particular on the impact of diabetes medications beyond blood glucose control. This is followed by 3 other articles developed by members of the steering committee that address risk factors in the patient with diabetes other than the magnitude of hyperglycemia. Dr. Patrick J. Boyle discusses mechanisms and mediators of macrovascular disease, which is substantially increased in patients with type 2 diabetes. Dr. Vivian A. Fonseca presents a rationale for the use of insulin sensitizers for the prevention of cardiovascular events. Dr. Theodore Mazzone discusses strategies for therapeutic intervention in the prevention of macrovascular events.

The review papers and summary statements presented in this supplement are designed to provide a clinically focused review of an increasingly important aspect of care.

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The risk of death from cardiovascular disease is high in patients with diabetes mellitus. Indeed, diabetes is the most prevalent factor putting US citizens at risk for cardiovascular events. In an attempt to focus on the role of effective decision-making in optimizing outcomes in patients with diabetes, a multidisciplinary steering committee, convened by Strategic Consultants International (Hemel Hempstead Herts, United Kingdom) and CME Consultants (Wakefield, Rhode Island, USA), developed a series of statements summarizing key points about the risks of macrovascular disease, its pathogenetic mechanisms in patients with diabetes, and the opportunities for, and optimal management of, cardiovascular risk. In developing these statements, the steering committee concentrated in particular on the impact of diabetes medications beyond glucose control. This article presents those statements, together with supporting evidence and more detailed exploration of their significance.

**IMPACT OF CARDIOVASCULAR DISEASE ON LIFE EXPECTANCY IN PATIENTS WITH DIABETES MELLITUS**

Statement 1: Patients with diabetes have an increased risk for cardiovascular disease that contributes to decreased life expectancy.

Patients with diabetes have an increased risk for cardiovascular disease, a risk that contributes to a significant decrease in life expectancy. The additional risk for cardiovascular disease also increases with advancing age. Patients with diabetes have a risk for an initial myocardial infarction...
A thrombotic event is the cause of death in 75% to 80% of patients with diabetes.2,3 Type 2 diabetes is associated with a 2- to 4-fold increased risk for cardiovascular disease.2,4–7 This increased risk is the main factor underlying the excess mortality and reduced life expectancy of people with type 2 diabetes; the life expectancy of a man or woman diagnosed with type 2 diabetes at the age of 40 is reduced by an estimated 8 years in comparison with individuals without diabetes.8 In a study of men taking medication for diabetes, the absolute risk of death ascribed to cardiovascular disease was higher than the risk in nondiabetic men in every age stratum, ethnic background, and risk factor level; among men with higher values for risk factors (serum cholesterol, systolic blood pressure, cigarette smoking) and their combinations, the absolute risk of death from cardiovascular disease was found to rise more steeply in men with diabetes than in their counterparts without diabetes.9 In a meta-analysis of 27 studies that reported total deaths from coronary heart disease according to diabetes status, the risk for fatal coronary heart disease was 3-fold higher in persons with type 2 diabetes than in those without the disease (5.4% vs. 1.6%); also, the relative risk for fatal coronary heart disease associated with diabetes was found to be 50% higher in women than it is in men.7 In patients with type 2 diabetes, age remains a risk factor for cardiovascular disease.9,10

A Finnish population-based study has shown that patients with diabetes without a previous MI have as great a risk for MI as individuals without diabetes with a previous MI (Figure 1).11 The 7-year incidence rates of MI (fatal and nonfatal) in subjects without diabetes were 18.8% in those with a previous MI and 3.5% in those without a history of MI; the corresponding rates in individuals with diabetes were 45.0% and 20.2%, respectively. Similarly, a study based on data pooled from 9 prospective epidemiologic studies in the United States found that women with diabetes but without known cardiovascular disease have a risk for fatal stroke that is similar to that of nondiabetic women with a history of stroke but otherwise similar risk factor profile, and substantially higher than that of nondiabetic women without known cardiovascular disease.5

**PROGNOSIS AFTER A CARDIOVASCULAR EVENT**

Statement 2: The prognosis after a cardiovascular event is poorer in a patient with diabetes than in a patient without diabetes.

Prognosis after a cardiovascular event has been shown to be worse for patients with diabetes than for those without diabetes for a range of variables, including survival after initial MI, the extent of heart failure associated with an MI, outcomes of coronary revascularization procedures, and mortality after thrombolytic therapy.12–18

Patients with diabetes have a greater risk of dying from an MI, whether an initial attack or a recurrence, than do those without diabetes.14 Among hospitalized patients with a first acute MI, type 2 diabetes is consistently associated with increased mortality and increased hospital admission for heart failure.19 In an Australian study in 5,322 patients with acute MI and no previous history of ischemic heart disease, age-adjusted 28-day fatality rates were significantly higher among women and men with diabetes than among those without diabetes (relative risk [RR], 1.56 for women and 1.25 for men).15 This increased risk for death in patients with diabetes remained after accounting for their poorer risk factor profiles. If they reached the hospital alive, patients with diabetes were less likely to survive compared with their nondiabetic counterparts. Similarly, in a Finnish study of patients experiencing their first MI, the 28-day mortality rate for hospitalized patients was significantly higher for
men (14.4%) and women (21.7%) with diabetes compared with nondiabetic individuals (8.8% for men and 7.8% for women); the risk for death within 1 year was also significantly higher for those with vs. those without diabetes (hazard ratio [HR], 1.38 for men and 1.86 for women). In addition, diabetes increases the risk for cardiovascular mortality in patients with heart failure secondary to ischemia. 

Case-fatality rates in patients experiencing a first stroke are higher in individuals with diabetes compared with nondiabetic persons. Diabetes is an independent predictor of death within 30 days of a first stroke and of later mortality. 

**MECHANISMS UNDERLYING THE INCREASED RISK FOR CARDIOVASCULAR EVENTS IN PATIENTS WITH DIABETES**

Statement 3: Putative mechanisms underlying the increased risk for cardiovascular events in patients with diabetes include insulin resistance, changes in endothelial function, dyslipidemia, chronic inflammation and release of mediators of inflammation, procoagulability, and impaired fibrinolysis. 

A variety of mechanisms underlies the increased risk for cardiovascular events in patients with diabetes. Insulin resistance in skeletal muscle decreases glucose disposal and the use of free fatty acids, leading to hyperglycemia and high levels of circulating free fatty acids and compensatory hyperinsulinemia. An excess of free fatty acids stimulates the overproduction of triglyceride-rich lipoprotein particles, including atherogenic very-low-density lipoprotein (VLDL) and a decrease in high-density lipoprotein (HDL). This dyslipidemia leads to endothelial dysfunction, a state of deficiency of nitric oxide and increase in mediators that promote vasoconstriction and accelerated formation, progression, and rupture of atherosclerotic lesions; endothelial dysfunction leads to further impairment of insulin action and a negative feedback cycle. Deposition of lipids, particularly low-density lipoproteins (LDLs), and oxidative stress in vessel walls causes release of inflammatory cytokines and adhesion molecules (such as interleukin-1, tumor necrosis factor–α, and vascular cell adhesion molecule–1), which instigate a chain of responses ultimately leading to foam cell formation and subsequent elaboration of atherosclerotic lesions vulnerable to rupture.

Results of studies of rats with diabetes suggest that collagen gene expression is increased in diabetes, leading to elaboration of the extracellular matrix. Decreased synthesis and activity of matrix metalloproteinases (MMPs) in diabetes may contribute to increased collagen deposition and pathologic remodeling in the arterial vasculature.

Elevated concentrations of glucose may induce discordant regulation of the MMP system in vascular cells. Increased activities of MMP-1, MMP-2, and MMP-9 induced by high glucose levels can lead to destabilization and promote matrix degradation, thereby accelerating atherogenesis and potentially reducing plaque stability. Plaques obtained from patients with diabetes contain more macrophages, which secrete MMPs, and less collagen compared with those from patients without diabetes, and are therefore thought to be less stable than plaques in patients without diabetes.

Type 2 diabetes and the metabolic syndrome (including insulin resistance) that often underlies it is a state of hypercoagulability characterized by increased platelet reactivity, augmented activity of the coagulation system, and impaired fibrinolysis; this leads ultimately to augmented atherosclerosis. Increases in circulating platelet aggregates, platelet aggregation in response to platelet agonists and platelet contractile force, and the presence of higher plasma levels of platelet-release products, such as β-thromboglobulin, platelet factor 4, and thrombomodulin, provide evidence of platelet hyperactivity in diabetes. Concentrations of various markers of activation of coagulation, such as prothrombin activation fragments 1 and 2 and thrombin–antithrombin complexes, are increased in patients with diabetes, as are the markers in plasma of risk factors for thrombosis (fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor). The fibrinolytic system—the primary means of removing clots—is less effective in diabetes because of the abnormal clot structures that are more resistant to degradation, and is suppressed as a result of high concentrations in blood of plasminogen activator inhibitor–1 (PAI-1). Expression and secretion of PAI-1 in vascular endothelial and smooth muscle cells is enhanced in patients with diabetes by insulin, proinsulin, proinsulin-like molecules, and VLDL triglyceride; in both atheroma specimens from patients undergoing coronary percutaneous transluminal coronary angioplasty and arterial wall tissue from patients undergoing coronary artery bypass graft surgery, concentrations of PAI-1 are substantially higher in samples from patients with diabetes than in those from patients without diabetes with a similar degree of cardiovascular disease.

**MANAGEMENT OF CARDIOVASCULAR DISEASE RISK FACTORS**

Statement 4: Many standard cardiovascular disease risk factors contribute to cardiovascular deterioration in patients with diabetes, including hypertension, dyslipidemia, hypercholesterolemia, and derangements in carbohydrate metabolism and insulin sensitivity. Management of these risk factors, for example with statins and antihypertensive therapy, has been shown to significantly reduce the incidence of cardiovascular events in patients with diabetes.

Cardiovascular disease in patients with diabetes involves several factors in addition to hyperglycemia, notably hypertension, dyslipidemia, and insulin resistance. Patients with diabetes typically have reduced blood concentrations of protective HDL cholesterol and increased triglycerides, and although they have near-normal or slightly elevated concentrations of LDL cholesterol, the small, dense LDL particles typical of type 2 diabetes are particularly susceptible to oxidative modification and thus may trigger inflam-
mation. Triglyceride-rich lipoproteins may activate nuclear factor–κB, a transcription factor mediating expression of inflammatory cytokines. Up to 60% of patients with type 2 diabetes have concomitant hypertension that accelerates the development of microvascular and macrovascular complications; even modest increases in blood pressure increase the risk for diabetic complications. In the Multiple Risk Factors Intervention Trial (MRFIT), in male patients aged 35–57 at high risk (as judged from a risk-factor combination of elevated cholesterol, hypertension, and cigarette smoking), cardiovascular mortality was increased 2- to 4-fold in patients with diabetes compared with those in the cohort without diabetes, and there was a clear association between systolic blood pressure and complications, without a threshold value.

Antihypertensive agents protect against cardiovascular complications in patients with diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), for example, tight control of blood pressure, with an achieved level of 144/82 mm Hg in comparison with a less stringent level of 154/87 mm Hg, was associated with a risk reduction in macrovascular disease (MI, sudden death, stroke, peripheral vascular disease) of 34% (P = 0.019). In the Hypertension Optimal Treatment (HOT) study, which investigated intensive blood pressure–lowering therapy and low-dose aspirin, lowering blood pressure was particularly beneficial in patients with diabetes, in whom there was a 51% reduction in major cardiovascular events in the group with target diastolic blood pressure ≤80 mm Hg compared with the ≥90-mm Hg target group (P = 0.005).

In the Heart Outcomes Prevention Evaluation (HOPE) study, compared with placebo, reduction of blood pressure in response to angiotensin-converting enzyme inhibitor therapy was associated with a 25% lower risk in the combined primary outcome of MI, stroke, or cardiovascular death (P = 0.0004) and a 37% lower risk of cardiovascular death. A meta-analysis of 27 randomized trials has suggested that different classes of blood pressure–lowering agents offer similar levels of reduction of cardiovascular risk and that the reduction of cardiovascular risk is comparable in individuals with and without diabetes; there was, however, some indication that lower blood pressure goals resulted in greater reductions in total major cardiovascular events in patients with diabetes than in those without diabetes.

Treatment of dyslipidemia significantly reduces cardiovascular risk in individuals with diabetes. The Heart Protection Study (HPS), for example, provided powerful evidence that therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the incidence of MI and stroke in patients with diabetes, even in those without manifest coronary disease or high cholesterol. In the Collaborative Atorvastatin Diabetes Study (CARDS), a placebo-controlled primary prevention study in high-risk patients with diabetes, therapy with statins was associated with a 37% (95% confidence interval [CI], 17% to 52%; P = 0.001) relative reduction in the risk of a first acute coronary heart disease event, coronary revascularization, or stroke. A comprehensive meta-analysis of published, unconfounded, randomized, prospective, placebo-controlled, double-blind clinical trials of lipid-lowering drug treatment (mostly statins) found that in patients with diabetes, therapy was associated with a risk reduction (relative to that seen with placebo) for a major coronary event of 21% (95% CI, 11% to 30%; P = 0.0001) in primary prevention studies and 21% (95% CI, 10% to 31%; P = 0.0005) in secondary prevention studies. The corresponding reductions for patients without diabetes, 23% (95% CI, 12% to 33%; P = 0.0003) and 23% (95% CI, 19% to 26%; P = 0.0005), suggest that lipid-lowering drug treatment is equally effective in patients with and without diabetes. However, because patients with diabetes are at higher risk for cardiovascular events than are patients without diabetes, even when treated these individuals remain at significantly higher risk (HR, 1.17; 95% CI, 1.05 to 1.30; P = 0.006) (Figure 2).

CORRECTION OF HYPERGLYCEMIA: IMPACT ON MACROVASCULAR AND MACROVASCULAR EVENTS

Statement 5: Elevated concentrations of glucose-define diabetes and drive the development of microvascular complications in the eyes and kidneys. Although correction of hyperglycemia can reduce macrovascular events, the coupling of normoglycemia is less tight for macrovascular events than it is for reduction of microvascular complications.

It is well established that hyperglycemia is a major contributor to microvascular disease, i.e., retinopathy, nephropathy, and neuropathy, in patients with diabetes. As shown in the Diabetes Control and Complications Trial (DCCT), a prospective trial in >1,440 patients with type 1 diabetes, intensive glycemic control significantly delays the onset of, and slows the progression of, such microvascular complications, providing benefits well beyond the discontinuation of the active intervention. Similarly, the UKPDS demonstrated the benefits of intensified glycemic control with metformin, sulfonylurea, or insulin on microvascular complications in newly diagnosed patients with type 2 diabetes, with a highly significant 25% risk reduction in microvascular end points.

Long-term follow-up data from the DCCT have shown that intensive glycemic control is linked to a 57% relative reduction in the risk for nonfatal MI, stroke, and death from cardiovascular disease in patients with type 1 diabetes. Although prospective studies in patients with type 2 diabetes have shown association between the degree of hyperglycemia and macrovascular complications, and epidemiologic data suggest reductions in glycosylated hemoglobin (HbA1c) are associated with a reduction in rates of MI (a 14% reduction for each 1% reduction in HbA1c), unequivocal evidence that intensive glycemic control reduces the risk for death from macrovascular disease is, as yet, lacking. In the UKPDS, intensive therapy with insulin or sulfonylureas was not associated with a statis-
tically significant reduction in cardiovascular events.\textsuperscript{49} Meta-analysis of randomized controlled trials, however, suggests that treatments designed to improve glycemic control reduce the incidence of macrovascular events in both type 1 and type 2 diabetes.\textsuperscript{54} More definitive evidence on this question should be provided by large, ongoing clinical trials such as Action to Control Cardiovascular Risk in Diabetes (ACCORD). It should be remembered, however, that the multiplicity of factors involved in the pathogenesis of type 2 diabetes make it somewhat unreasonable to expect that strict glycemic control alone will be sufficient to completely ameliorate atherosclerosis.

SCREENING AND INTERVENTION FOR RISK FACTORS IN PATIENTS WITH DIABETES MELLITUS

Statement 6: Patients with diabetes should be carefully screened for additional risk factors for acute coronary syndrome/MI. Appropriate interventions should be adopted, with the goal of reducing the incidence of these events and improving survival.

Self-monitoring of blood glucose is an integral part of the management of diabetes and the achievement of stable glycemic control. HbA\textsubscript{1c} should be assessed at least twice yearly to ascertain efficacy of antidiabetic therapy: The target for HbA\textsubscript{1c} is <7%, or as low as possible without unacceptable hypoglycemia.\textsuperscript{55} Other cardiovascular risk factors, including dyslipidemia, hypertension, obesity, smoking, family history of premature coronary disease, microalbuminuria, and macroalbuminuria, should be assessed at least annually in patients with diabetes.\textsuperscript{55} Patients at increased risk for coronary heart disease should be treated with antiplatelet agents (e.g., aspirin).

Blood pressure should be measured in patients with diabetes at every regularly scheduled visit.\textsuperscript{55} The target blood pressure level in patients with diabetes is <130/<80 mm Hg, or lower if the patient can tolerate it. Patients with a blood pressure level >140/90 mm Hg should be treated with a pharmacologic agent of a class that has been demonstrated to reduce cardiovascular events in patients with diabetes. Multiple drug therapy should be used if necessary to achieve blood pressure targets.\textsuperscript{55}

Tests for lipid disorders should be carried out at least once a year. In patients without overt cardiovascular disease, the goal is to achieve an LDL cholesterol level <100 mg/dL (1 mg/dL = 0.02586 mmol/L) or, in those aged >40 years, to achieve a reduction in LDL cholesterol of 30% to 40% with statin treatment, irrespective of the baseline level. All patients with diabetes and overt cardiovascular disease should be treated with a statin to reduce LDL cholesterol by 30% to 40%. Triglyceride levels should be <150 mg/dL (1 mg/dL = 0.01129 mmol/L) and HDL cholesterol levels should be >40 mg/dL in men and >50 mg/dL in women.\textsuperscript{55} Numerous “nontraditional” risk factors for cardiovascular disease, such as insulin resistance, increased concentrations in blood of markers of inflammation, homocysteine, and postprandial hyperglycemia, are thought to exist in patients with diabetes.\textsuperscript{56} Several of these can be assessed in clinical practice, and some therapies already in use affect some of these nontraditional risk factors; there is, in general, however, insufficient evidence as yet that routine testing for such factors improves diagnosis or the outcome of therapy.\textsuperscript{56}

INSULIN SENSITIZERS: IMPACT ON SURVIVAL AND INCIDENCE OF CARDIOVASCULAR EVENTS

Statement 7: Results of observational and interventional studies have indicated that some insulin sensitizers appear to reduce the incidence of cardiovascular events and improve survival.

Evidence that insulin sensitizers reduce the incidence of cardiovascular events and improve survival was provided by the UKPDS, in which patients treated with the biguanide metformin, an agent that reduces hepatic glucose output and hence the hyperglycemia driving compensatory hyperinsulinemia, experienced a significant reduction in the risk for
MI in comparison with conventional therapy. The risk reduction effected by metformin could not be explained solely on the basis of better glycemic control. In a retrospective study of patients with diabetes discharged from the hospital after an acute MI, those treated with a combination of metformin and an insulin sensitizer, a thiazolidinedione (TZD), were at significantly lower risk of mortality than patients prescribed a regimen not including an insulin sensitizer (HR, 0.52; 95% CI, 0.34 to 0.82). In another case-control study that looked at outcomes in patients after a first MI, patients on TZD or metformin monotherapy were at significantly reduced risk for recurrent MI compared with those receiving sulfonylurea monotherapy; the addition of a TZD to sulfonylurea therapy, but not the addition of metformin, significantly reduced MI risk.

**IMPACT OF THIAZOLIDINEDIONE TREATMENT ON CARDIOVASCULAR EVENTS**

Statement 8: Thiazolidinediones have beneficial effects on metabolism that may improve cardiovascular risk. A randomized clinical trial in patients with advanced atherosclerosis indicates that the addition of pioglitazone to therapy deemed to be optimal for glycemic control may reduce the incidence of cardiovascular events such as MI and stroke over a 3-year interval and may be associated with an overall reduction in all-cause mortality.

TZDs and biguanides have different mechanisms of action and different metabolic effects. Metformin acts primarily by decreasing endogenous glucose production from the liver. In contrast, TZDs increase overall insulin sensitivity by altering the effects of fat on insulin action. TZDs have a small effect of reducing hepatic glucose production and a larger effect of increasing skeletal muscle glucose disposal. For example, the TZD troglitazone appears to be twice as effective as metformin at enhancing insulin-mediated glucose disposal. Since many cardiovascular risk factors are modulated by insulin/insulin resistance, agents that substantially improve sensitivity to insulin may have particular potential to improve such risk factors. Unlike metformin, TZDs reduce blood pressure and some TZDs (e.g., pioglitazone, troglitazone) have favorable effects on lipids, increasing HDL level and LDL particle size; TZDs also have beneficial effects on nontraditional cardiovascular risk factors (fibrinogen, PAI-1, and C-reactive protein) that are not seen, or are less marked, with metformin (Table 1).

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial was a large-scale randomized, placebo-controlled trial of pioglitazone in 5,238 patients with type 2 diabetes and documented advanced atherosclerosis. The primary end point of the trial was time from randomization to all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndromes, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle. Of the 5,238 patients recruited, 2,605 received pioglitazone and 2,633 received placebo. Patients were followed for an average of 34.5 months. At least 1 event from the primary composite end point was recorded in 514 (19.7%) of the patients in the pioglitazone group and 572 (21.7%) of the patients in the placebo group, equating with 3-year Kaplan-Meier estimates of 21.0% and 23.5%, respectively; however, this difference was not statistically significant (HR, 0.90; 95% CI, 0.80 to 1.02; \( P = 0.095 \)).

The primary endpoint of the PROactive trial was a composite of all-cause mortality, nonfatal MI (excluding silent MI), and stroke. There was a statistically significant benefit of pioglitazone on this end point: 3-year Kaplan-Meier estimates of the event rate (all-cause mortality, nonfatal MI excluding silent MI, or stroke) were 12.3% with pioglitazone and 14.4% with placebo (HR, 0.84; 95% CI, 0.72 to 0.98; \( P = 0.027 \)). Additon of pioglitazone to existing therapy in 1,000 patients would avoid an estimated 21 first MIs, strokes, or deaths over 3 years, i.e., 48 patients would need to be treated for 3 years to avoid 1 first major cardiovascular event. It is of note that this benefit over placebo was achieved in these high-risk patients by the addition of pioglitazone to what was considered to be optimal glycemic therapy (blood glucose was being managed by diet alone targets (in part explaining the increased use of insulin and metformin in the placebo group over the duration of the trial). This background medication included glucose-lowering therapy (blood glucose was being managed by diet alone in only 4% of patients at baseline), as well as antiplatelet (85% of patients), antihypertensive, and lipid-altering (43% of patients were being treated with statins and 10% with fibrates at baseline) therapies.

Of the patients recruited into the PROactive trial, 46.7% had experienced an MI 6 months previously. Such patients are at very high risk for a subsequent macrovascular event. Preplanned subanalysis of this group revealed further statistically significant benefits of pioglitazone. The time to fatal or nonfatal MI (excluding silent MI) in these patients was significantly delayed by pioglitazone; the risk for

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Potential antiatherosclerotic effects of thiazolidinediones</th>
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<tbody>
<tr>
<td>Effect</td>
<td>Direction of Effect</td>
</tr>
<tr>
<td>Smooth muscle irritability</td>
<td>↓</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>↓</td>
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<tr>
<td>Vascular smooth muscle nitric oxide</td>
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<td>Fibrinogen</td>
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<tr>
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<tr>
<td>Circulating free fatty acids</td>
<td>↓</td>
</tr>
<tr>
<td>LDL particle size</td>
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</tbody>
</table>

HDL = high-density lipoprotein; IL = interleukin; LDL = low-density lipoprotein; TNF = tumor necrosis factor; ↑ = increased; ↓ = decreased.

*Not consistent with thiazolidinediones.
recurrent fatal/nonfatal MI was reduced by 28% (HR, 0.72; 95% CI, 0.52 to 0.99; P = 0.045). Pioglitazone also reduced the risk for acute coronary syndromes by 37% in this subgroup of patients (HR, 0.63; 95% CI, 0.41 to 0.97; P = 0.035). A statistically significant advantage for pioglitazone over placebo was also seen for a composite cardiac end point of cardiac death, nonfatal MI, coronary revascularization, and acute coronary syndromes (HR, 0.81; 95% CI, 0.66 to 0.98; P = 0.034).63 It is estimated that adding pioglitazone to existing medication in 1,000 patients with previous MI would prevent 22 recurrent MIs and 23 acute coronary syndrome events over 3 years.

Of the total 5,238 patients recruited into the PROactive trial, 984 (18.8%) had experienced a stroke ≥6 months before study entry. In this subgroup of patients, pioglitazone added to existing therapy affected a statistically significant 47% reduction in the risk for recurrent fatal or nonfatal stroke (HR, 0.53; 95% CI, 0.34 to 0.85; P = 0.008).64 Additionally, in patients with a previous stroke given pioglitazone, time to cardiovascular death, nonfatal stroke, or nonfatal MI was significantly prolonged (HR, 0.72; P = 0.047). Results in the PROactive trial have indicated that addition of pioglitazone to existing “optimal” therapy in patients with type 2 diabetes and atherosclerotic disease, particularly those who have had a previous MI or stroke and are at risk of experiencing a subsequent macrovascular event, may have clinical benefits.

Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of edema and heart failure. Edema is often seen with all TZDs and is sometimes attributable to exacerbation of overt or occult heart failure, but may occur in the absence of and independent of heart failure as a result of effects of TZDs on renal tubular function and hydrostatic effects related to reduction of blood pressure.65 Unfortunately, many physicians equate the presence of edema seen with TZDs with heart failure when in fact the two may be dissociated. Conventional diuretics are not very effective for treatment of the edema seen with TZDs; because of the site of action of TZDs at the renal tubule, amiloride may be beneficial. Reduction of the TZD dose may diminish edema. In view of these and other considerations, the presence of edema with TZDs should raise the suspicion of occult or overt heart failure that should be evaluated objectively and managed appropriately and conventionally. Dosage of TZDs may have to be diminished, or the drug discontinued if edema is a problem or the induction of edema is exacerbating or precipitating heart failure. Otherwise, continuation with judicious use of the drugs may well be appropriate.

Acknowledgments

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Diabetes Mellitus and Macrovascular Disease: Mechanisms and Mediators

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ABSTRACT

Atherosclerosis is a chronic inflammatory condition initiated in the endothelium in response to injury and maintained through the interactions between modified lipoproteins, macrophages, and arterial wall constituents. Risk for macrovascular disease is substantially increased in patients with type 2 diabetes mellitus. Factors underlying the link between insulin resistance/type 2 diabetes and macrovascular disease include reduced adiponectin concentration, increased expression of vascular cell adhesion molecule–1 and consequent adhesion of T-lymphocytes to the coronary endothelium, procoagulability with increased expression of plasminogen activator inhibitor–1 (PAI)-1, and instability of atherosclerotic plaques resulting from increased expression by macrophages of matrix metalloproteinases (MMPs). Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor (PPAR)–γ and increase adiponectin. TZD therapy is associated with decreases in hepatic fat content and glycosylated hemoglobin and an increase in hepatic glucose disposal. TZDs lower circulating free fatty acid concentration and triglyceride content in the liver, but not in skeletal muscle. Effects of PPAR-γ agonists in vitro and in animal models provide evidence for additional potential antiatherosclerotic benefits in patients with diabetes beyond the treatment of hyperglycemia and dyslipidemia, including the reduction of expression of macrophage MMPs and scavenger receptor-1, and indirect reduction of PAI-1 and inhibition of vascular smooth muscle cell proliferation, via suppression of type 1 angiotensin-2 receptor expression. Dual PPAR-α/γ agonists, retinoid receptor agonists, and, to a lesser extent, TZDs, also stimulate cholesterol efflux from macrophages in vitro. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Adiponectin; Atherosclerosis; Macrovascular disease; Peroxisome proliferator-activated receptor; Thiazolidinedione; Type 2 diabetes mellitus

Atherosclerosis is a chronic inflammatory condition initiated in the endothelium in response to injury and maintained through the interactions between modified lipoproteins, particularly low-density lipoprotein (LDL) cholesterol, T-lymphocytes, monocyte-derived macrophages, and the normal constituents of the arterial wall. The initial step in the disposal of LDL cholesterol across the endothelium is an oxidative one, driven by angiotensin II, a biochemical marker produced by the endothelium (Figure 1). Angiotensin II is not an oxidizing enzyme, but it sets up the metabolic milieu favoring excess production of superoxide radicals that permit LDL oxidation. This LDL oxidation step triggers a chain of metabolic responses, the first of which is infiltration of the subendothelial compartment with monocytes that, under the influence of interleukin (IL)–1 from the endothelium, differentiate into macrophages. These macrophages avidly engulf oxidized LDL, via the scavenger receptor (SRA)–1, ultimately turning into foam cells. The uptake of oxidized LDL by macrophages induces them to produce macrophage colony-stimulating factor, which stimulates macrophage proliferation, and IL-2 and tumor necrosis factor (TNF)–α, which in turn stimulate production of vascular cell adhesion molecule (VCAM)–1 on the coronary endothelial surface. VCAM-1 promotes the adherence of circulating T-lymphocytes to the coronary endothelium. Following arrival in the subendothelial space, these lympho-
cytes produce interferon-γ, which drives resident smooth muscle cell proliferation. Proliferation of smooth muscle cells in the intima is followed by elaboration of the extracellular matrix and accumulation of cross-linked collagen and proteoglycans, generating an atherosclerotic lesion with a thick fibrous cap.

The vast majority of patients with diabetes mellitus die of causes related to atherosclerosis. The precursor state, the metabolic syndrome, affects millions of individuals in the United States, and some 7% of the population have diagnosed diabetes.\(^1\) The metabolic syndrome, also known as the insulin resistance syndrome, is a cluster of specific cardiovascular disease risk factors with underlying pathology related to insulin resistance and dysregulation of fatty acid metabolism.\(^2\) There are 5 main factors, the “deadly quintet,” that contribute to the oxidative stress and endothelial dysfunction that underlie the dysmetabolic syndrome: hypertension, hyperlipidemia, obesity, procoagulability, and hyperglycemia.

**INSULIN RESISTANCE: A MITOCHONDRIAL DEFECT**

The basis of insulin resistance has been investigated in the young, lean, insulin-resistant offspring of a parent or grandparent with type 2 diabetes, i.e., individuals unlikely to have other confounding factors.\(^3\) In comparison with insulin-sensitive control subjects matched for age, height, weight, and physical activity, insulin-resistant individuals showed moderate but statistically significant hyperglycemia and hyperinsulinemia before and during a glucose tolerance test, although there was no significant difference between the 2 groups in the basal rate of liver glucose production or fasting plasma fatty acid concentration. The insulin-resistant subjects had a significantly lower glucose disposal rate (the amount of glucose per kilogram that needs to be infused to keep systemic glucose normal against a fixed amount of infused insulin) compared with the control group (3.3 ± 0.3 mg/kg per min vs. 7.7 ± 0.5 mg/kg per min; \(P < 0.001\)). It appears that, in the early decades of life at least, an increase in insulin secretion that reduces glucose production by the liver compensates for this defect in glucose disposal. The intramyocellular lipid content of insulin-resistant subjects was 80% higher than in the control subjects. This increase in intramyocellular lipids is most probably attributable to mitochondrial dysfunction, given that insulin-resistant individuals had a rate of muscle adenosine triphosphate (ATP) synthesis approximately 30% lower than that of the control subjects (\(P = 0.01\)), but no significant differences from the control group in systemic or localized rates of lipolysis or in plasma concentrations of adipokines. These findings are consistent with the concept that insulin resistance is associated with accumulation of free fatty acids in myocytes owing to an inherited (or acquired) defect in mitochondrial fat oxidation, and that hyperglycemia in insulin-resistant individuals and
patients with type 2 diabetes arises from poor glucose disposal resulting from low rates of mitochondrial fatty acid oxidation.

**THE ROLE OF ADIPONECTIN**

If insulin resistance is the result of a mitochondrial defect, what, then, are the implications for cardiovascular disease? Adipose tissue plays an important role in insulin resistance through the production and secretion of a variety of proteins, including TNF-α, plasminogen activator inhibitor (PAI)-1, resistin, components of the renin-angiotensin system, and adiponectin, that may modulate insulin sensitivity and glucose and lipid metabolism. Of these, adiponectin is of particular interest, as it has insulin-sensitizing activity, increasing muscle fatty acid oxidation and glucose uptake. Adiponectin contains a collagen-like domain and a globular domain: protease-mediated cleavage of the molecule generates a globular segment that enhances fatty acid oxidation in muscles. Adiponectin is the most abundant protein product of the adipocyte and, with a plasma concentration of 2 to 17 μg/mL in healthy volunteers, represents about 0.01% of total plasma protein. In obese, insulin-resistant animal models, expression of adiponectin, in contrast to that of other adipokines such as TNF-α and resistin, is decreased rather than increased. In obese patients, production of adiponectin is reduced and plasma adiponectin concentrations are inversely correlated with the severity of insulin resistance. Furthermore, plasma adiponectin levels are lower in individuals with type 2 diabetes than in age- and body mass index (BMI)–matched controls, and, among patients with diabetes, is lower in those with coronary artery disease. Low adiponectin concentrations contribute to low rates of muscle fat oxidation.

Genetic mapping has identified 1 locus for genetic susceptibility to type 2 diabetes and the metabolic syndrome at chromosome 3q27, the location of the adiponectin gene. Screening of patients with type 2 diabetes and comparison with age- and BMI-matched control subjects for mutations in the adiponectin gene has identified 4 missense mutations, all in the globular domain: R112C, I164T, R221S, and H241P. The frequency of 1 of these mutations, I164T, was 2.0% in patients with type 2 diabetes compared to 1.7% in age- and BMI-matched control subjects for mutations in the adiponectin gene. Eicosanoids and fatty acids activate all 3 PPAR subtypes, but the presumed endogenous PPAR ligand, the prostaglandin D2 metabolite 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), is selective for PPAR-γ. Adiponectin, underlies, at least in part, the pathophysiology of insulin resistance.

**ADIPONECTIN AS A THERAPEUTIC TARGET**

Adiponectin has antiatherogenic properties. It appears to be an antagonist of TNF-α, counteracting its proinflammatory effects on arterial walls, and, in isolated human coronary endothelium, inhibits TNF-α–mediated adhesion of monocytes and induction of VCAM-1. Because binding to VCAM-1 is required for T-lymphocytes to gain access to the subendothelial space, increased adiponectin concentrations could reduce subendothelial inflammation and oppose atherosclerotic processes.

Apolipoprotein (apo) E–deficient transgenic mice lack apoE, without which LDL is not cleared from the circulation; these mice are hypercholesterolemic and, early in life, spontaneously develop foam cell lesions and fibrous plaques at the sites typically affected in human atherosclerosis. Overexpression of adiponectin can be achieved in apoE-deficient mice by injecting them with recombinant adenovirus-expressing adiponectin. ApoE-deficient mice raised normally for 12 weeks before the onset of injections with adiponectin-expressing adenovirus showed a 48-fold rise in plasma adiponectin at 14 weeks in comparison with control mice; the increase in plasma adiponectin resulting from this treatment was associated with a 30% decrease in inflammatory lesions in the aortic sinus. Plasma cholesterol, glucose, and insulin levels were unaffected by the treatment. Immunohistochemical staining revealed that adiponectin was colocalized with lesional macrophages in the injured artery. Cells cultured from aortic tissue from the treated mice had significantly suppressed expression of VCAM-1 and SRA-1, and there was reduced accumulation of lipids in macrophages in the atherosclerotic lesions. TNF-α concentration was also reduced, though not significantly. This study was the first to demonstrate in vivo that increasing adiponectin reduces atherosclerosis by attenuating endothelial inflammatory responses and transformation of macrophages to foam cells.

**RAISING ADIPONECTIN VIA PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR ACTIVATION**

The promoter sequence for the adiponectin gene contains a peroxisome proliferator-activated receptor (PPAR)–γ response element. PPARs, of which there are 3 subtypes (α, β, and γ), are ligand-activated transcription factors that act as mediators of inflammatory responses and regulators of lipid metabolism. PPARs form a functional heterodimer with the retinoid X receptor (RXR)–α and bind to specific DNA sequences in the promoter regions of target genes, such as the adiponectin gene. Eicosanoids and fatty acids activate all 3 PPAR subtypes, but the presumed endogenous PPAR ligand, the prostaglandin D2 metabolite 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), is selective for PPAR-γ. Adiponectin expression is increased in adiporeactive and insulin-resistant animal models and human subjects. The increased expression of adiponectin results from increased production or improved secretion, or both, of adiponectin.
expressed predominantly in adipose tissue, but PPARs are also expressed in the vasculature and in leukocytes. PPAR activators inhibit the induced expression of VCAM-1 and monocyte binding to human aortic endothelial cells, suggesting that they may be of benefit in ameliorating the chronic inflammation underlying atherosclerosis.

Thiazolidinediones (TZDs) are insulin-sensitizing agents that increase glucose disposal in muscle and suppress gluconeogenesis in the liver. They are used for the treatment of type 2 diabetes, and are highly selective PPAR-γ agonists. Three TZDs (pioglitazone, troglitazone, and rosiglitazone) have been introduced into clinical use in the United States. Troglitazone was withdrawn from the market because of an adverse effect that appears to have been a unique idiosyncratic end-stage liver disease, which was not observed with pioglitazone or rosiglitazone. Based on head-to-head comparisons of the 2 currently available compounds, pioglitazone appears to have a superior effect on raising HDL (15% vs. 7.8% increase), whereas rosiglitazone raises apolipoprotein by 10.5% (according to the same head-to-head randomized investigation), but pioglitazone has no effect. Because there is only a copy of apoB on each LDL particle, this would suggest that LDL particle number could rise in patients treated with rosiglitazone; the nuclear magnetic resonance measurements of this parameter confirm this suspicion. In 1 study conducted after the withdrawal of troglitazone, subjects were randomly converted from troglitazone to either rosiglitazone or pioglitazone. No difference was noted in hemoglobin A1c depending on which TZD was used. However, the conversion from troglitazone to pioglitazone was associated with a >5% decrease in LDL concentration, whereas converting from troglitazone to rosiglitazone had little effect on LDL levels. As nuclear transcription activators, each compound has a different profile of gene activation and suppression, which may partially explain the differences noted above.

The binding to PPAR-γ in adipose tissue promotes adipocyte differentiation, resulting in an increase in the number of small, insulin-sensitive adipocytes and an associated decrease in serum-free fatty acid levels and TNF-α expression. TZDs, via binding to the PPAR-γ response element in the promoter region of the adiponectin gene, activate adiponectin gene transcription, increasing plasma adiponectin levels. The TZD pioglitazone has been shown to effect a 3-fold increase in plasma adiponectin concentration in patients with type 2 diabetes that is associated with a decrease in hepatic fat content and increased hepatic insulin sensitivity (Figure 2). The increase in insulin sensitivity effected by TZDs is probably mediated, at least in part, through an increase in plasma adiponectin.

ADDITIONAL EFFECTS OF PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR ACTIVATION

Prostaglandin D2 metabolites are major products of arachidonic acid metabolism in macrophages, and PPAR-γ can be identified in monocytes and macrophages from human atherosclerotic lesions but not in normal artery specimens. In vitro, the expression of markers of macrophase activation, nitric oxide synthase, matrix metalloproteinase (MMP)-9 (gelatinase B), and SRA-1, is inhibited by activation of PPAR-γ using a TZD or 15d-PGJ2. Although the uptake of oxidized LDL by macrophages via SRA-1 is initially protective, progressive accumulation eventually leads to foam cell formation and atherosclerotic lesion progression. Activation of PPAR-γ using TZDs is a potential means by which to suppress SRA-1 gene transcription and hence inhibit the uptake of oxidized LDL.
RXR-α agonists can induce similar responses to PPAR ligands by activating the PPAR/RXR heterodimer.\textsuperscript{30} RXR agonists induce expression of ATP-binding cassette protein–I (ABC-1) in macrophages in vitro.\textsuperscript{31} ABC-1 is a cell membrane transporter that translocates phospholipids and cholesterol to the cell surface where they interact with apolipoproteins, forming HDL particles that dissociate from the cell.\textsuperscript{32} RXR activation of macrophages stimulates ABC-1–mediated cholesterol efflux from macrophages in vitro.\textsuperscript{31}

The development of atherosclerosis was significantly reduced in apoE-deficient mice given an RXR agonist (LG100364) or a dual PPAR-α/γ agonist (GW2331) in their daily diet from 8 to 10 weeks of age. Animals given a PPAR-γ–selective agonist, the TZD rosiglitazone, showed a significant but less marked delay in the development of lesions, with an 18% reduction in lesion area.\textsuperscript{31}

PROCOAGULABILITY AND PLAQUE RUPTURE

The ultimate problem in atherosclerosis is plaque rupture, thrombosis, and major vessel occlusion. The driving factor for this increased risk in diabetes is procoagulability, an increase in platelet aggregation, coupled with an increase in plasma concentrations of PAI-1 and other thrombotic factors.\textsuperscript{33} Insulin, proinsulin-like molecules, glucose, and very-low-density lipoprotein directly stimulate transcription and secretion of PAI-1 in endothelial and smooth muscle cells. Immunohistochemical investigation of arterial wall specimens from patients undergoing coronary artery bypass graft surgery has indicated that patients with diabetes have twice the level of PAI-1–related immunofluorescence despite having the same degree of cardiovascular disease as patients without diabetes.\textsuperscript{34}

Angiotensin II is a positive regulator of PAI-1 production and also stimulates vascular smooth muscle cell proliferation.\textsuperscript{35} PPAR-γ activators, both TZDs and 15d-PGJ₂, but not PPAR-α activators, suppress expression of the type 1 angiotensin II receptor (AT-R1) at the level of transcription in vascular smooth muscle cells.\textsuperscript{36} This offers a potential means by which to intervene in the atherosclerotic process, because it is smooth muscle cells that are largely responsible for the increase in PAI-1 in diabetes. Reducing AT-R1 expression with TZDs should theoretically attenuate the overproduction of PAI-1 in patients with diabetes and reduce the potential for thrombosis.

Atherosclerotic plaques are stabilized by the elaboration of the extracellular matrix by proliferating vascular smooth muscle cells. Plaques are destabilized, however, by the MMPs released by macrophages; these enzymes degrade the cross-linking collagen fibrils, promoting plaque rupture. Activation of PPAR-γ in human monocyte–derived macrophages in vitro decreases levels and activity of MMP-9 (the main metalloproteinase secreted by macrophages in vitro).\textsuperscript{28} Experiments in U937 cells, leukemic cells that express PPAR-γ and can be induced to differentiate into macrophage-like cells by treatment with the phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA), show that TPA treatment increases MMP-9 gene promoter activity and that this increased activity is strongly inhibited by concurrent PPAR-γ activation using 15d-PGJ₂.\textsuperscript{29} Overexpression of PPAR-γ in these cells potentiated the inhibitory effect of 15d-PGJ₂ on MMP-9 gene expression, consistent with the effect being mediated by PPAR-γ activation and a role for PPAR-γ in regulation of MMP-9 activity in vivo.

SUMMARY

The link between insulin resistance/type 2 diabetes and cardiovascular disease is based on procoagulability. Angiotensin II is a positive regulator of PAI-1 production and also stimulates vascular smooth muscle cell proliferation.

Expression of AT-R1 can be suppressed by PPAR-γ activators, including TZDs. Atherosclerotic plaques are destabilized by MMPs released by macrophages. Activation of PPAR-γ is strongly inhibited by concurrent PPAR-γ activation. Finally, there are low adiponectin concentrations, which contribute to the proatherogenic state. Increasing plasma adiponectin concentrations, therefore, could have antiatherogenic effects by reducing the inflammatory responses and transforming macrophages to foam cells. PPAR-γ activators have also been shown to increase adiponectin by activating gene transcription. TZD therapy may have an impact well beyond the treatment of hyperglycemia and dyslipidemia and should be considered as a potentially exploitable means of reducing coronary artery disease.

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Rationale for the Use of Insulin Sensitizers to Prevent Cardiovascular Events in Type 2 Diabetes Mellitus

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ABSTRACT

Cardiovascular events in patients with type 2 diabetes mellitus are a major problem in clinical practice, and patients with diabetes have derived less benefit from advances in preventive and interventional cardiology. Tighter goals for metabolic management and attention to nontraditional risk factors may be needed in this patient group. Insulin resistance rather than hyperinsulinemia is thought to underlie cardiovascular disease in patients with diabetes. Insulin resistance is associated with cardiovascular events and a wide range of traditional and nontraditional risk factors for cardiovascular disease (e.g., endothelial dysfunction, dyslipidemia, inflammation, vascular wall abnormalities). Therapy with lifestyle modifications, metformin, or thiazolidinediones (TZDs) corrects many of the abnormalities associated with diabetes in addition to lowering blood glucose and correcting diabetic dyslipidemia. TZDs, acting via the peroxisome proliferator-activated receptor-γ, affect a number of mediators involved in the development of the cardiovascular complications of diabetes, including lipid profiles, vascular changes, and inflammatory mediators. TZDs decrease plasminogen activator–1 and C-reactive protein levels. They also reduce the extent of thickening of the carotid artery and reduce hyperplasia after coronary stent implantation. Insulin-sensitizing therapy with TZDs is a promising intervention for patients with diabetes at risk for adverse cardiovascular outcomes. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Hyperinsulinemia; Insulin; Insulin sensitizer; Thiazolidinedione; Type 2 diabetes mellitus

Cardiovascular events in patients with type 2 diabetes mellitus are a major problem in clinical practice. There have been important advances in preventive and interventional cardiology over the past 20 years that have resulted in a significant reduction in cardiovascular events and mortality in the general population. The National Health and Nutritional Examination Survey (NHANES) recruited 2 cohorts 10 years apart and followed them. A highly significant 36% reduction in mortality was demonstrated in male patients without diabetes. In contrast, mortality for male patients with diabetes decreased by a nonsignificant 13%; in female patients without diabetes, mortality decreased by 27%, whereas in female patients with diabetes it actually increased by 23%. Thus, it is important to find alternative strategies to reduce the burden of cardiovascular disease and mortality in individuals with diabetes.

Various organizations, including the American Diabetes Association (ADA), have recommended goals for reduction of risk factors for cardiovascular disease in persons with diabetes. The goal for hemoglobin A1c is <7%, although it is now recommended that normoglycemia may be a more appropriate target, provided the patient does not become hypoglycemic. Similarly, the goal for blood pressure is <130/80 mm Hg. These goals, and those for lipid abnormalities, are summarized in Table 1. To achieve all of these goals, a multifactorial risk-reduction strategy is needed, requiring complex multidrug therapy. Such a strategy has been tested in 1 small study comparing conventional intervention involving multiple risk factors with an intensive, targeted, multifactorial intervention approach involving be-
behavior modification. Although the ADA targets were not achieved in this trial, the significantly greater reductions in risk factors in the intensive targeted therapy group translated into a 53% reduction in cardiovascular disease endpoints over a 7-year period (Figure 1).

The “traditional” risk factors (hyperglycemia, hyper tension, and hyperlipidemia) do not fully account for the increased mortality from cardiovascular disease in persons with type 2 diabetes, and therefore investigators have attempted to determine whether other targets for therapy are appropriate. These include the so-called nontraditional risk factors, such as insulin resistance, and the many other risk factors that are frequently associated with it (Table 2).

The purpose of this review is to highlight the association of insulin resistance with these nontraditional risk factors, which serve as surrogate markers for cardiovascular disease, and to determine the impact of insulin-sensitizer therapy on these risk factors. These data have provided a rationale for carrying out large multicenter clinical trials investigating the effect of insulin sensitizers on cardiovascular events and mortality.

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<td>Dyslipidemia</td>
<td>Low-density lipoprotein cholesterol</td>
<td>Patients with diabetes mellitus: &lt;100 mg/dL.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very-high-risk patients with diabetes and cardiovascular disease: &lt;70 mg/dL</td>
</tr>
<tr>
<td></td>
<td>High-density lipoprotein cholesterol</td>
<td>Men: &gt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: &gt;50 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>&lt;150 mg/dL</td>
</tr>
</tbody>
</table>

Adapted from Diabetes Care.

*To convert values to SI units: for plasma glucose, 1 mg/dL = 0.05551 mmol/L; for cholesterol, 1 mg/dL = 0.02586 mmol/L; for triglycerides, 1 mg/dL = 0.01129: mmol/L.

Figure 1 Reduction in cardiovascular end points (death from cardiovascular causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic arterial disease) with intensive, targeted, multifactorial therapy and conventional therapy addressing multiple risk factors in the Steno-2 study. CI = confidence interval. (Reprinted with permission from N Engl J Med.)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Conventional therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of Follow-up</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>80</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>80</td>
<td>78</td>
<td>74</td>
</tr>
</tbody>
</table>

P = 0.007
Hazard ratio = 0.47
(95% CI, 0.24–0.73; P = 0.008)
With both insulin resistance and atherosclerosis. These findings provide a mechanistic link between insulin resistance and atherosclerosis.

Established Risk Factors | Nontraditional Risk Factors
---|---
Hypertension | Insulin resistance
Lipids | Abnormal fibrinolysis (plasminogen activator inhibitor–1)
Obesity | Endothelial dysfunction
Smoking | Microalbuminuria
Glucose | Markers of inflammation (C-reactive protein)
Glucose | Vascular wall abnormalities
Glucose | Hypercoagulation
Glucose | Postprandial hyperglycemia

**ASSOCIATION OF INSULIN RESISTANCE WITH NONTRADITIONAL RISK FACTORS**

Examination of the NHANES III database has demonstrated that nontraditional risk factors are common in persons with diabetes. Indeed, ≳ 1 nontraditional risk factor was found to be present in approximately 25% of people with normal glucose tolerance. This rate increased to 40% among individuals with impaired glucose tolerance and to >60% in those with type 2 diabetes. When the analysis was carried out using the National Cholesterol Education Program (NCEP)–defined metabolic syndrome, approximately 30% of patients without the metabolic syndrome had ≳ 1 of these risk factors, compared with almost 50% of patients with the metabolic syndrome. Several studies have demonstrated that many of these nontraditional risk factors are associated with both insulin resistance and atherosclerosis. These findings provide a mechanistic link between insulin resistance and atherosclerosis.

**HYPERINSULINEMIA AS A RISK FACTOR**

Several studies have demonstrated that hyperinsulinemia is a risk factor for cardiovascular disease. Perhaps the most important of these is the Quebec Heart Study, which demonstrated that hyperinsulinemia was a risk factor for cardiovascular disease in patients classified as low risk as well as those classified as high risk on the basis of their cholesterol levels. Indeed, not only was hyperinsulinemia a risk factor independent of cholesterol, it seemed to have an additive effect with cholesterol as a predictor of risk for cardiovascular disease. Hyperinsulinemia has been shown to be associated with several other risk factors for cardiovascular disease, including hypertension, elevated triglycerides, and low levels of high-density lipoprotein (HDL) cholesterol, in addition to type 2 diabetes.

Indeed, the association of hyperinsulinemia with cardiovascular disease has led to the perception that insulin may be a cause of vascular disease. This theory also derives from basic science studies demonstrating the multiple signaling pathways of insulin in a variety of cell types. A defect in glucose metabolism leads to a decrease in nitric oxide production, and the resultant hyperinsulinemia stimulates other processes less affected by the signaling abnormality, such as the mitogen-activated protein kinase (MAPK) pathway that stimulates vascular cell growth. However, the conclusion that insulin is a cause of vascular disease comes in part from flawed analyses of studies in patients with longstanding diabetes treated with insulin, who have increased cardiovascular risk and events. Actually, much of this increased risk can be accounted for by the duration of diabetes and the age of these patients rather than treatment with insulin. In fact, large long-term studies have shown no increase in cardiovascular events in people treated with insulin, and recent studies have demonstrated benefits of insulin treatment to cardiovascular risk.

Thus, hyperinsulinemia is not the cause of the atherosclerosis, but rather a marker of underlying insulin resistance. Perhaps the most clear-cut evidence demonstrating the lack of iatrogenic effect of insulin on cardiovascular disease comes from the Diabetes Control and Complications Trial (DCCT) follow-up study Epidemiology of Diabetes Interventions and Complications (EDIC) in patients with type 1 diabetes, in which intensive treatment with insulin (often requiring more frequent injections) led to a significant reduction in cardiovascular events compared with those treated conventionally.

**VASCULAR STUDIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS**

Several studies have demonstrated a nitric oxide production or action defect in patients with diabetes. Nitric oxide is a potent vasodilator released by the endothelium that plays a pivotal role in maintaining vascular homeostasis. Decreased release or activity of nitric oxide could contribute to abnormalities in vasomotor function. Vascular reactivity in the forearm is decreased not only in patients with diabetes, but also in those with impaired glucose tolerance and even in relatives of persons with diabetes. Recent studies have demonstrated that the myocardial blood flow response to stimuli is impaired in individuals with insulin resistance compared with patients with insulin sensitivity.

It is also now widely recognized that insulin regulates the enzyme nitric oxide synthase, and that insulin infusions lead to dose-dependent increases in leg blood flow. This effect of insulin on the vasculature is impaired in insulin-resistant states such as type 2 diabetes and obesity, and these abnormalities appear to be closely related to insulin resistance in terms of glucose metabolism.

A large epidemiologic study has demonstrated that obesity is associated with abnormal vascular reactivity, with flow-mediated dilatation (FMD) increasing with increasing body mass index (BMI) up to approximately 30, after which any increase in BMI is associated with a decline in FMD in the brachial artery.

Another abnormality that is well recognized in diabetes and insulin resistance is an increased thickness of the ca-
Figure 2  Potential atherogenic and antiatherogenic actions of insulin in vascular cells. IRS = insulin resistance syndrome; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein/extracellular signal-regulated kinase; NO = nitric oxide; PI 3-kinase = phosphatidylinositol 3-kinase; PKC = protein kinase C. (Adapted from Lancet.9)

Figure 3  Intensive treatment, involving more frequent insulin injections, is associated with a reduced risk of cardiovascular (CV) disease in patients with type 1 diabetes mellitus. MI = myocardial infarction. (Reprinted with permission from N Engl J Med.12)
Inflammation has now become recognized as an early abnormality in the natural history of atherosclerosis. Several studies have demonstrated that markers for inflammation such as C-reactive protein (CRP) are elevated in obese individuals, and chronic subclinical inflammation is recognized as being part of the insulin resistance syndrome. It is now recognized that adipose tissue may play an important role in the development of low-grade systemic inflammation. Adipose tissue secretes a number of cytokines (e.g., tumor necrosis factor [TNF]–α, interleukin [IL]–1, and IL-6) that stimulate inflammatory protein production in the liver through activation of nuclear factor (NF)–κB, which is a key step in the development of inflammation. NF-κB is an important regulator of nuclear gene transcription, and its activation leads to increased expression of a number of genes involved in the development of type 2 diabetes and coronary artery disease. Another marker of inflammation involved in the pathogenesis of vascular disease is plasminogen activator inhibitor (PAI)–1; PAI-1 activity is increased in patients with obesity and in those with type 2 diabetes. Currently, there is good evidence that chronic inflammation precedes the onset of type 2 diabetes, and this may be a marker for the future development of not only diabetes but also cardiovascular events.

**EFFECT OF INTERVENTIONS ON NONTRADITIONAL RISK FACTORS**

Several studies have documented that interventions that improve insulin sensitivity also reduce some of the nontraditional risk factors for cardiovascular disease. Plasma CRP levels decrease after weight loss in obese women. Other inflammatory markers have been shown to improve with diet and exercise. Endothelial function can be assessed by measuring FMD; FMD is abnormal in obesity, rising with BMI (up to 30). FMD has been shown to improve after modest changes in lifestyle that include some degree of weight loss coupled with regular exercise.

**Insulin Sensitizers**

Interest in insulin sensitizers to prevent microvascular disease and MI arose after publication of the United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated a reduction in the incidence of MI associated with metformin that could not be explained by the drug’s effects on glucose alone. Metformin is a weak insulin sensitizer, and it was postulated that a more powerful insulin sensitizer might have even better effects.

Thiazolidinediones (TZDs), which include pioglitazone and rosiglitazone, are approved for the treatment of type 2 diabetes and have a beneficial and prolonged effect on glycemia. Pioglitazone has also been shown to improve the lipid profile, with a decrease in triglycerides and an increase in HDL cholesterol. There has been much interest in the effect of TZDs on the nontraditional risk factors for cardiovascular disease, including their ability to improve vascular reactivity. Pioglitazone decreases urine albumin excretion and endothelin-1 concentration. Several studies have demonstrated that TZDs decrease PAI-1 and CRP.

Studies have attempted to differentiate between various TZDs and their effects on a variety of peroxisome proliferator-activated receptor (PPAR)–responsive genes using microarray analysis. Although such differences clearly exist in vitro, their significance in human disease and their relation to drug benefits or toxicity remain speculative. The only difference observed between the drugs in the TZD class appears to be in relation to the lipid profile discussed, and the impact of those differences on cardiovascular events also remains unclear. TZD therapy also has beneficial effects on thickening of the carotid artery wall, which is a well-recognized abnormality in patients with diabetes and insulin resistance. A small study has demonstrated a reduction in carotid intima-media thickness (CIMT) in response to pioglitazone treatment. These results were confirmed in a large, randomized, multicenter trial in which pioglitazone significantly delayed progression of CIMT in comparison with glimepiride. This study is discussed in detail by Mazzone elsewhere in this supplement. TZDs have also been shown to improve nontraditional risk factors in persons without diabetes. These findings may have implications if TZDs were to be used for the prevention of diabetes; studies in patients with prediabetes show them to delay the onset of the disease.

TZDs have improved success rates in small studies of patients undergoing balloon angioplasty and stent implants, situations in which individuals with diabetes have particularly poor outcomes. Pioglitazone has been shown to decrease new intimal hyperplasia after coronary stent insertion (Figure 4). Similarly, rosiglitazone has been shown to decrease restenosis. Mechanisms underlying the decreased intimal hyperplasia associated with TZD therapy have been elucidated in insulin-resistant rats; treatment with a TZD decreased intimal hyperplasia by decreasing smooth muscle cell growth and inflammation via activation of PPAR-γ. PPAR-γ activation by the
TZDs has a range of beneficial effects on the risk factors for cardiovascular disease in patients with diabetes. The overall impact of pioglitazone on cardiovascular outcomes in this patient group has been investigated in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study (reviewed elsewhere in this supplement).\textsuperscript{35,41,42}

Evidence is accumulating, therefore, that insulin-sensitizing therapy translates into clinical benefit in patients with diabetes. A retrospective study that showed a mortality benefit with combined insulin-sensitizing therapies in \(8,872\) patients (mean age, \(76.4\) years) discharged on glucose-lowering medication. \textit{MET} = metformin; \textit{TZD} = thiazolidinedione. (Reprinted with permission from \textit{Diabetes Care}.)\textsuperscript{43}

**SUMMARY**

Insulin resistance is associated with cardiovascular events and a wide range of traditional and nontraditional risk factors for cardiovascular disease. Insulin-sensitizing therapy...
with lifestyle modification, metformin, or TZDs has clearly demonstrated a reduction in these cardiovascular risk factors. Prospective clinical trials are expected to shed further light on the role of insulin-sensitizing therapy in reducing cardiovascular morbidity and mortality in patients with diabetes. The multiple effects of TZDs, which extend beyond glucose control, make them a promising interventional therapy for patients with diabetes who are at risk for cardiovascular complications (Table 3).

### References


### Table 3: Effect of insulin sensitizing therapy on cardiovascular risk factors

<table>
<thead>
<tr>
<th>Effect</th>
<th>Direction of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle irritability</td>
<td>↓</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>↓</td>
</tr>
<tr>
<td>Vascular smooth muscle nitric oxide</td>
<td>↓</td>
</tr>
<tr>
<td>Platelet reactivity</td>
<td>↓</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td>↓</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↓</td>
</tr>
<tr>
<td>IL-6, TNF-α, C-reactive protein</td>
<td>↓</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>↓</td>
</tr>
<tr>
<td>Circulating free fatty acids</td>
<td>↓</td>
</tr>
<tr>
<td>LDL particle size</td>
<td>↓</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; IL = interleukin; LDL = low-density lipoprotein; TNF = tumor necrosis factor; ↑ = increased; ↓ = decreased.
*Not consistent with thiazolidinediones.


Prevention of Macrovascular Disease in Patients with Diabetes Mellitus: Opportunities for Intervention

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ABSTRACT

Individuals with diabetes mellitus are at considerably higher risk for coronary artery disease compared with individuals without diabetes. In the United States, diabetes is the most prevalent factor putting patients at risk for coronary events. Intensive control of blood glucose has been demonstrated to reduce the risk for cardiovascular disease in patients with type 1 diabetes, but this has yet to be proved in patients with type 2 diabetes. Aggressive management of established cardiovascular risk factors using blood pressure-lowering and lipid-lowering therapies (particularly the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins) has been conclusively shown to reduce cardiovascular risk in patients with type 2 diabetes. Patients with type 2 diabetes remain at residual excess risk compared with individuals without diabetes, such that there is still a need for novel therapeutic approaches. Thiazolidinediones (TZDs) may have beneficial effects on cardiovascular disease in diabetes beyond improving blood glucose control. Although the evidence regarding rosiglitazone is yet to mature, completed and ongoing clinical trials with pioglitazone suggest that this TZD may be a novel treatment for managing cardiovascular risk in patients with diabetes. Addition of pioglitazone to existing therapy in high-risk patients with diabetes and atherosclerotic disease improves cardiovascular outcomes, and may be particularly beneficial for patients with previous myocardial infarction or stroke. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Atherosclerosis; Clinical trial; Macrovascular disease; Pioglitazone; Thiazolidinedione; Type 2 diabetes mellitus

In 2003, 14.1 million Americans had physician-diagnosed diabetes mellitus, and a further 6 million were estimated to have undiagnosed diabetes.1 Patients with diabetes are at high risk for coronary artery disease. Indeed, with 13.2 million US individuals with established coronary heart disease, and 5.5 million with past stroke, diabetes is the most prevalent factor putting Americans at risk for coronary events. Compared with nondiabetic patients, the risk for coronary artery disease is increased 2- to 4-fold, and patients with diabetes but without a previous myocardial infarction (MI) may be at as great a risk for MI as are nondiabetic patients with a previous MI.2 There are multiple potential mechanisms underlying the increased risk for atherosclerosis in patients with diabetes, including the dyslipidemia/hyperlipidemia that accompanies insulin resistance (and which is not completely treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor [statin] therapy), increases in proinflammatory factors, such as tumor necrosis factor (TNF)–α, a shift in the fibrinolysis–fibrinogen balance that promotes thrombosis, glycation of proteins, and hypertension.3 Therefore, a variety of potential therapeutic strategies might be used to manage cardiovascular risk in patients with type 2 diabetes.

CONTROL OF BLOOD GLUCOSE

In patients with type 1 diabetes, intensive control of blood glucose, involving ≥3 injections of insulin per day with dose adjustments based on glucose measurements and goals, has been shown to reduce the long-term incidence of cardiovascular disease.4 Compared with conventional treatment (1 to 2 daily insulin injections and avoidance of hypoglycemia/hyperglycemia), intensive treatment reduced...
the risk for any cardiovascular disease event by 42% and the risk for nonfatal MI, stroke, or death from cardiovascular disease by 57% (mean follow up, 17 years). Although it has been demonstrated that intensive diabetes therapy designed to lower blood glucose reduces the risk for retinopathy, nephropathy, and neuropathy in both type 1 and type 2 diabetes, confirmatory evidence from prospective intervention trials that such therapy reduces cardiovascular risk in type 2 diabetes is still lacking.6

BLOOD PRESSURE–LOWERING THERAPY

Although intensive control of blood glucose has yet to be proved to reduce cardiovascular risk in patients with type 2 diabetes, several studies have demonstrated the beneficial effect of managing hypertension for reducing cardiovascular events in patients with diabetes. The treatment of hypertension in patients with diabetes has been shown to reduce cardiovascular mortality in many trials using a variety of antihypertensive agents (Table 1).6 There is limited evidence that patients with diabetes achieve a greater reduction compared with those without diabetes in terms of the risk for major cardiovascular events and cardiovascular death through blood pressure–lowering regimens targeting lower blood pressure goals. In head-to-head comparisons, agents from different drug classes—angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, angiotensin receptor blockers (ARBs), and diuretics/β-blockers—do not demonstrate significant benefits over one another, and the various ARBs all have a similar magnitude of effect compared with control treatment. The important factor, therefore, is to reach the target blood pressure; the means by which this is achieved is somewhat less important in terms of cardiovascular risk.

MANAGEMENT OF DYSLIPIDEMIA

A series of well-designed prospective studies have demonstrated that aggressive management of low-density lipoprotein (LDL) cholesterol reduces cardiovascular risk. The Heart Protection Study (HPS) was designed to evaluate the long-term effects of cholesterol-lowering therapy on vascular and nonvascular mortality and major morbidity, on the basis that, across the range of LDL cholesterol blood concentrations encountered in Western populations, lower concentrations are associated with lower cardiovascular disease risk.7 This study was a 5-year, prospective, randomized, placebo-controlled trial of simvastatin in >20,500 adults in the United Kingdom, aged 40 to 80 years, at substantial 5-year risk for death from coronary heart disease owing to history of coronary disease, other occlusive arterial disease, or diabetes; 5,963 of the patients had diabetes. The mean nonfasting blood concentration of LDL cholesterol before treatment was 3.4 mmol/L (approximately 130 mg/dL). Simvastatin treatment was associated with an average difference from placebo of 1.0 mmol/L or 38 mg/dL (2.3 mmol/L [89 mg/dL] for the statin group and 3.3 mmol/L [128 mg/dL] for the placebo group) and a significant reduction of 27% in the incidence of major coronary events in the simvastatin group. Patients with diabetes experienced the same reduction in risk for cardiovascular events with simvastatin treatment as did those without diabetes (Figure 1).7

Among the 2,912 patients with diabetes who had no previous occlusive heart disease, there was a 33% reduction in cardiovascular events, providing the first real evidence that lowering blood LDL cholesterol in patients with diabetes but without diagnosed coronary disease is clinically beneficial.7,8

The Collaborative Atorvastatin Diabetes Study (CARDS), followed on from the HPS and was a study of primary prevention of cardiovascular disease specifically in patients with diabetes.9 The trial recruited patients with no previous history of cardiovascular disease, blood LDL cholesterol ≤4.14 mmol/L (160 mg/dL), fasting triglycerides ≤1.78 mmol/L (≤600 mg/dL) and ≥1 of the following risk factors: retinopathy, albuminuria, current smoking, or hypertension. The cholesterol-lowering statin treatment produced a 37% reduction in risk for the primary end point, namely, the first occurrence of an acute coronary heart disease event, coronary revascularization, or stroke. Acute coronary heart disease events were reduced by 36%, coronary revascularizations by 31%, and stroke by 48%. These 2 studies provided powerful evidence that management of lipid abnor-

Table 1 Meta-analysis of the effect of blood pressure control on cardiovascular outcomes in diabetes mellitus

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ACE-Inhibitor vs. Placebo</th>
<th>Ca Antagonist vs. Placebo</th>
<th>Angiotensin Receptor Blocker vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.69 (0.55–0.86)</td>
<td>0.47 (0.28–0.78)</td>
<td>0.96 (0.77–1.19)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0.91 (0.62–1.34)</td>
<td>0.60 (0.41–0.89)</td>
<td>0.92 (0.72–1.17)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.88 (0.67–1.16)</td>
<td>1.29 (0.97–1.72)</td>
<td>0.70 (0.59–0.83)</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>0.80 (0.71–0.89)</td>
<td>0.72 (0.34–1.53)</td>
<td>0.90 (0.82–0.99)</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>0.67 (0.55–0.82)</td>
<td>0.54 (0.21–1.42)</td>
<td>0.99 (0.77–1.28)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.76 (0.65–0.89)</td>
<td>0.83 (0.65–1.06)</td>
<td>0.91 (0.75–1.10)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CI = confidence interval.
Adapted from Arch Intern Med.6
malities with statin therapy reduces cardiovascular risk in diabetes.

Because diabetes is particularly associated with decreases in high-density lipoprotein (HDL), there has also been interest in the use of peroxisome proliferator-activated receptor (PPAR)-α agonists (fibrates) as HDL-raising agents. Reduction in total and LDL cholesterol and an increase in HDL cholesterol have been reported to result from fenofibrate treatment, with associated reduction in the progression of atherosclerosis in patients with diabetes. A more rigorous evaluation of the usefulness of fibrates in diabetic dyslipidemia was undertaken in the Fenofibrate Intervention and Event-Lowering in Diabetes (FIELD) study in which the impact of 5 years of fenofibrate therapy on cardiovascular disease events was investigated in 9,795 patients with type 2 diabetes. Although this trial found no significant benefit of fenofibrate on the primary composite end point, death from coronary heart disease or nonfatal MI (10.4 coronary events per 1,000 person-years at risk with fenofibrate vs. 11.7 with placebo), there was a significant difference between fenofibrate and placebo in the principal secondary end point, total cardiovascular disease events (25.8 vs. 29.0 events per 1,000 person-years at risk, respectively). This benefit was primarily a result of reduction in the rate of coronary revascularization in the fenofibrate group (11.9 vs. 15 events per 1,000 person-years at risk; \( P = 0.003 \)). Fenofibrate was not associated with a significant benefit in terms of total mortality or cardiovascular disease mortality. There was a difference in use of statins between the fenofibrate and placebo groups during the trial. Present evidence does not warrant a recommendation for increased use of fenofibrate in patients with diabetes.

However, the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, evaluating treatment with fenofibrate versus placebo in 10,000 patients with diabetes treated with simvastatin and followed for 6 years, should provide more conclusive evidence on the efficacy of fenofibrate with regard to cardiovascular events and mortality.

**NOVEL APPROACHES: THIAZOLIDINEDIONES**

Patients with diabetes experience a reduction in cardiovascular risk from therapy designed to correct dyslipidemia or hypertension similar to that in patients without diabetes. However, because they are at intrinsically higher risk than patients without diabetes, treated patients with diabetes still carry a residual excess risk compared with treated patients without diabetes. In a meta-analysis of primary prevention trials of lipid-lowering therapy (Figure 2), the risk reduction was the same in patients with diabetes and in those without diabetes, but treated patients with diabetes remained at significantly higher risk for experiencing a major coronary event compared with the treated patients without diabetes (hazard ratio [HR], 1.17; \( P = 0.006 \)). The same was true in secondary prevention trials for lipid-lowering therapy (HR, 1.59; \( P < 0.00001 \)) and also of antihyper-

tensive therapy. There is, therefore, still a need for additional novel therapies to manage cardiovascular risk in patients with diabetes. One class of drugs that is promising in this regard is the thiazolidinediones (TZDs).

The TZDs – pioglitazone, troglitazone, and rosiglitazone – are PPAR-γ agonists. In addition to exerting glycemic control via insulin sensitization, they have actions that directly or indirectly improve a range of cardiovascular risk factors, such as ameliorating endothelial dysfunction, decreasing smooth muscle cell irritability, platelet reactivity, fibrinogen, plasminogen activator inhibitor–1, and inflammatory markers (interleukin-6, TNF-α, C-reactive protein), and increasing vascular smooth muscle levels of nitric oxide. They also induce favorable changes in lipid balance, increasing plasma HDL cholesterol, decreasing circulating free fatty acids and triglycerides, and improving the LDL subfraction distribution. These effects are exerted at a cellular or molecular level and are likely to be independent of the effects on glycemic control. Importantly, TZDs reduce atherosclerosis in nondiabetic, atherosclerosis-prone mouse models, independent of any effects on lipids or glycemia.

The first large, cardiovascular outcome-based clinical trial of a TZD to be reported was the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study. This was a 3-year secondary prevention trial assessing the efficacy of pioglitazone (versus placebo) added to existing therapy in reducing macrovascular morbidity and mortality in 5,238 high-risk patients with type 2 diabetes and evidence of macrovascular disease. The primary end point of the trial was a composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndromes, and cardiac intervention, including coronary artery bypass graft or percutaneous coronary intervention, leg revascularization, and amputation above the ankle. Patients recruited were aged 35 to 75 years, with glycosylated hemoglobin (HbA1c) concentration >6.5% despite existing treatment with diet alone or with oral glucose-lowering agents with or without insulin, and evidence of extensive macrovascular disease (MI or stoke ≥6 months previously, acute coronary syndromes ≥3 months previously, or objective evidence of coronary artery disease or obstructive arterial disease in the leg). Patients received oral pioglitazone titrated from 15 mg to 45 mg (n = 2,605) or matching placebo (n = 2,633). Patient characteristics were similar in the 2 groups. The mean age overall was 61.8 years, with a median time since diagnosis of diabetes of 8 years. At randomization, 62% of patients were taking metformin and 62% were taking sulfonylurea as monotherapy or in combination; >30% of patients were receiving insulin.

The average time of observation was 34.5 months, with 16% of the pioglitazone group and 17% of the placebo group discontinuing study medication before death or final visit. Kaplan-Meier analysis of the time to the primary end point indicated pioglitazone therapy was associated with a statistically nonsignificant 10% risk reduction (HR, 0.90;
95% confidence interval [CI], 0.8 to 1.02). There was, however, a statistically significant 16% risk reduction (HR, 0.84; 95% CI, 0.72 to 0.98; \( P < 0.027 \)) in the pioglitazone group for the principal secondary end point, a composite of all-cause mortality, nonfatal MI (excluding silent MI), and stroke.

Several subgroup analyses of the PROactive trial have now been carried out. Among the patients included in the trial, 2,445 (46.7%) had experienced an MI \( \geq \) 6 months before randomization, 1,230 from the pioglitazone group and 1,215 from the placebo group. A prespecified analysis of this subgroup indicated that pioglitazone therapy was associated with a significant delay, compared with placebo, in time to fatal or nonfatal MI (excluding silent MI) (HR, 0.72; 95% CI, 0.52 to 0.99; \( P = 0.045 \)) (Figure 3).\(^{23} \)

Post hoc analysis of the same subgroup also revealed a significant benefit of pioglitazone over placebo in time to a composite cardiac end point, including cardiac death, nonfatal MI, coronary revascularization, and acute coronary syndromes (HR, 0.81; 95% CI, 0.66 to 0.98; \( P = 0.034 \)).\(^{23} \)

Another prespecified subgroup analysis included subjects with a previous stroke. Of the PROactive cohort, 984 patients (18.8%) had experienced a stroke \( \geq \) 6 months before study randomization, 486 in the pioglitazone group and 498 in the placebo group. Among these patients, pioglitazone treatment was associated with a statistically significant reduction in risk for recurrent stroke, relative to placebo, of 47% (HR, 0.53; 95% CI, 0.34 to 0.85; \( P = 0.008 \)) (Figure 4).\(^{24} \) A multivariate analysis of 25 prespecified baseline characteristics plus an additional 12 factors showed that prior stroke was the strongest predictor of recurrent stroke in the entire cohort of patients (HR, 2.88; \( P < 0.0001 \)). Use of pioglitazone (\( P = 0.008 \)) and statins (\( P = 0.013 \)) were the only factors with a significant effect on the risk for recurrent stroke in patients with previous stroke. Age (\( P = 0.0002 \)), HbA\(_{1c} \) \( \geq \) 7.5% (\( P = 0.0038 \)), creatinine \( \geq \) 130

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**Figure 1** Reduction in major cardiovascular events by diabetes mellitus status as a result of simvastatin therapy in the Heart Protection Study (HPS). CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction. (Reprinted with permission from *Lancet*.)

**Figure 2** Meta-analysis of primary prevention trials of lipid-lowering therapy (with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [statins] or fibrate) in patients with and without diabetes mellitus, showing event rate for major coronary events over a mean weighted follow-up of 4.5 years. Results are shown as hazard ratios (HRs) with 95% confidence intervals (CIs) in parentheses. Reductions in risk are comparable for patients with diabetes (21%; 95% CI, 11% to 30%; \( P < 0.0001 \)) compared with patients without diabetes (23%; 95% CI, 12% to 33%; \( P = 0.0003 \)). (Reprinted with permission from *BMJ*.)
and peripheral arterial disease \((P = 0.0092)\) were significant positive predictors of having a first stroke in patients without a previous stroke.

Carotid intima-media thickness (CIMT) measurement is a useful and well-validated surrogate end point for cardiovascular events.\(^{25}\) CIMT is strongly correlated with risk for future cardiovascular events, changes in CIMT over time are further predictive, and progression of CIMT has been used successfully as a marker of clinical benefit in clinical trials of statins.\(^{25,26}\) Small-scale studies of the effect of TZDs on CIMT have provided inconsistent results, but a large-scale, randomized, comparator-controlled study has recently demonstrated the benefits of pioglitazone in delaying the progression of CIMT in patients with type 2 diabetes.\(^{27}\) This trial (the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone [CHICAGO] trial) included 462 adults from the multiethnic metropolitan area of Chicago who were treated for 72 weeks with pioglitazone (15 to 45 mg/day) or glimepiride (1 to 4 mg/day).\(^{27}\) The patients were without clinical coronary artery disease, and were either newly diagnosed with type 2 diabetes or were being treated with diet and exercise, sulfonylurea, metformin, insulin, or a combination of these treatments; most were taking an oral diabetes treatment regimen and most were being treated for hypertension and lipid abnormalities. The primary end point, mean absolute change from baseline to final visit in posterior-wall CIMT of the left and right common carotid arteries, was significantly different between the 2 groups: $-0.001 \text{ mm}$ with pioglitazone versus $0.012 \text{ mm}$ with glimepiride (difference, $0.013 \text{ mm}$; 95% CI, $0.024 \text{ mm}$ to $-0.002 \text{ mm}$; \(P = 0.02\)). Pioglitazone was also associated with a significant benefit over glimepiride in terms of progression of maximum CIMT ($0.002 \text{ mm}$ vs. $0.026 \text{ mm}$ at 72 weeks; \(P = 0.008\)) (Figure 5).\(^{27}\)

The effect of pioglitazone in patients with type 2 diabetes and coronary artery disease is being further investigated in the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial, which is due to report in 2008. This trial has a design similar to CHICAGO and is expected to enroll a total of 440 patients undergoing coronary artery angiography randomized to receive pioglitazone or glimepiride and followed for 18 months; the primary end point of this trial is the change in coronary artery atheroma volume, measured by intravascular ultrasound.

A recently conducted meta-analysis assessed the effect of rosiglitazone on cardiovascular deaths and MI.\(^{28}\) This meta-analysis screened 116 trials, of which 48 met the

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inclusion criteria of being comparator-controlled, having a similar treatment duration in each treatment group, and >24 weeks of therapy; 6 of these studies were excluded because no cardiovascular deaths or MIs were reported. Within the remaining 42 trials, a total of 86 cases of MI were reported in the 14,376 patients who received rosiglitazone, compared with 72 MIs in the 44,635 patients receiving a comparator, resulting in an overall odds ratio of 1.43 (95% CI, 1.03 to 1.98; \( P = 0.03 \)). A nonsignificant trend was also reported for cardiovascular death (39 in 10,936 patients receiving rosiglitazone compared with 22 in 9,509 patients receiving a comparator) with an odds ratio of 1.64 (95% CI, 0.98 to 2.74; \( P = 0.06 \)). The authors point out, however, that their research relied on the publicly available data, not original source data. Furthermore, these trials were not designed to assess cardiovascular end points and were often of a relatively short duration with few events, resulting in wide confidence intervals. Moreover, with the exception of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, the events were not centrally adjudicated. It should also be noted that the 2 most reliable trials pending the results of the cardiovascular outcomes trial Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD), are the A Diabetes Outcome Prevention Trial (ADOPT) and DREAM trials. ADOPT compared rosiglitazone, metformin, and glyburide as initial therapy for type 2 diabetes in 4,360 patients. There were 27 cases of MI reported in 1,456 patients receiving rosiglitazone compared with 41 in 2,895 patients receiving metformin or glyburide, a nonsignificant difference, and there were numerically fewer deaths from cardiovascular causes (2 of 1,456 [0.14%] with rosiglitazone vs. 5 of 2,895 [0.18%] with metformin or glyburide). The DREAM trial assessed the effect of rosiglitazone compared with placebo in preventing or delaying the onset of diabetes. This placebo-controlled trial in 5,000 patients used central adjudication of cardiovascular events and reported no significant difference in MI (15 of 2,365 in the rosiglitazone arm vs. 9 of 2,634 in the placebo arm), providing an HR of 1.66 (95% CI, of 0.73 to 3.80; \( P = 0.2 \)), and no significant difference in cardiovascular death (0.5% in the rosiglitazone arm compared with 0.4% in the placebo arm), with an HR of 1.20 (95% CI, 0.52 to 2.77; \( P = 0.7 \)).

**SUMMARY**

Diabetes is a powerful risk factor for MI. Aggressive blood pressure and lipid control are established approaches for managing cardiovascular risk. Patients with diabetes remain, however, at residual excess risk for macrovascular disease in comparison with patients without diabetes. TZDs, in addition to their glucose-lowering effects, have several actions that may improve cardiovascular risk. Results from recently completed and ongoing trials suggest a potential role for pioglitazone as a novel treatment for managing cardiovascular risk in patients with diabetes. Addition of pioglitazone to therapy in patients with type 2 diabetes and atherosclerotic disease significantly reduces the risk for mortality, nonfatal MI, and stroke, and may be particularly beneficial in patients with previous MI or stroke who are at high risk for subsequent macrovascular events. Clarification of the effects of rosiglitazone is awaited.
References


CME ASSESSMENT TEST

Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action

Please circle the correct response to each question on the Answer Sheet provided. A passing score of \( \geq 70\% \) must be achieved to receive CME credit.

1. Which of the following statements is false?
   a. Patients with diabetes mellitus have a 2- to 4-fold increased risk for cardiovascular disease.
   b. Patients with diabetes have reduced life expectancy.
   c. Diabetes is a lower risk factor for myocardial infarction (MI) than is a history of previous MI.
   d. Diabetes worsens the prognosis after a cardiovascular event.

2. Which of the following statements about adiponectin is true?
   a. It has insulin-sensitizing activity.
   b. It is an inflammatory cytokine.
   c. It is raised in the plasma of obese individuals.
   d. It decreases uptake of glucose by skeletal muscle.

3. Which of the following statements is true?
   a. Hyperinsulinemia is a cause of atherosclerosis.
   b. In patients with diabetes, the recommended goal for hemoglobin A1c is \(<8\%\).
   c. Long-term insulin therapy increases the risk for cardiovascular disease.
   d. Hyperinsulinemia is a marker of insulin resistance.

4. Insulin resistance is associated with
   a. reduced intramyocellular lipid content
   b. raised basal hepatic glucose production
   c. a genetic defect in mitochondrial fat oxidation
   d. all of the above

5. Which of the following is not a “nontraditional” risk factor for cardiovascular disease in patients with diabetes?
   a. Endothelial dysfunction
   b. Hypertension
   c. Insulin resistance
   d. Increased plasminogen activator inhibitor–1 expression

6. Which of the following statements is true?
   a. Angiotensin receptor blockers are more effective than calcium antagonists in reducing cardiovascular events in patients with diabetes.
   b. Although effective as a secondary preventive strategy, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy has not been proved to reduce the rate of major coronary events in patients with diabetes who do not have evidence of existing macrovascular disease.
   c. The ability of fibrate therapy to reduce coronary revascularization procedures and cardiovascular mortality rates has been demonstrated in clinical trials in patients with diabetes.
   d. Weight reduction and exercise programs reduce plasma C-reactive protein in obese individuals.

7. Which of the following does peroxisome proliferator-activated receptor (PPAR)–\( \gamma \) activation increase?
   a. Expression of matrix metalloproteinase–9 by macrophages
   b. Expression of macrophage scavenger receptor–1
   c. Expression of vascular cell adhesion molecule–1 at the endothelial surface
   d. Plasma adiponectin

8. Which of the following statements about thiazolidinediones (TZDs) is true?
   a. TZDs have no effect on plasma high-density lipoprotein.
   b. TZDs decrease vascular smooth muscle nitric oxide.
   c. TZDs increase peripheral glucose disposal.
   d. TZDs are activators of PPAR–\( \alpha \).

9. In a clinical trial in patients with diabetes and established macrovascular disease, pioglitazone has been shown to
   a. have no effect on the risk for stroke recurrence
   b. reduce risk for death/nonfatal MI/stroke by 16%.
   c. reduce the risk for MI recurrence
   d. Both b and c

10. Progressive increase in carotid intima-media thickness in patients with diabetes
    a. is unaffected by pioglitazone therapy.
    b. is limited by TZD therapy.
    c. is accelerated by statin therapy.
    d. has shown no utility in clinical trials assessing cardiovascular risk.

September 2007  THE AMERICAN JOURNAL OF MEDICINE® Vol 120 (9B) S37
Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action

Instructions: (1) Please read the entire CME activity carefully. (2) Complete the Assessment Test by circling the correct answer to each question on the Answer Sheet below. Be sure to retain a copy of your answers for your files. (3) Answer all questions on the Evaluation Form, and return it with your Answer Sheet to the address below. Please note: a CME certificate will be issued only upon receipt of your completed Evaluation Form. (4) Once you have completed the Assessment Test and Evaluation Form, please note in the space provided on the Registration Form the amount of time it took you to complete the entire activity, including the posttest and evaluation.

Please complete the Answer Sheet and Evaluation Form and post or fax to:

CME Consultants
94 Main Street
Wakefield, Rhode Island 02879
Fax: (401) 789-4366

ANSWER SHEET (circle the best answer to each question)

1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d

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REGISTRATION FORM

Please complete this section legibly.

* First Name ___________________________ MI _____ Last Name ___________________________

* Degree ___________________________ Medical Specialty ___________________________

* Mailing Address ___________________________ Room/Suite ___________________________

* City ___________________________ * State _________________ * Zip Code _________________

Phone No. ____________________ Fax No. ____________________ E-mail ____________________

* Certificate Type (Check one)  □ Physician  □ Nurse  □ Pharmacist  □ Other ____________________

May we contact you in the future to participate in a short postactivity evaluation?

□ Yes  □ No

I attest that I have completed the Optimizing Cardiovascular Outcomes in Diabetes Mellitus: A Call to Action activity as designed.

* Total time (hours in 0.25 increments) spent on this activity _______________________

* Signature ___________________________ Date ___________

* Indicates required information.

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CME Consultants is committed to excellence in continuing education. Your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please reflect carefully and complete this Evaluation Form. Please note: a CME certificate will be issued only upon receipt of your completed Evaluation Form.

Please answer the following questions by circling or checking the appropriate rating:

Scale: 1 = Poor 2 = Fair 3 = Good 4 = Excellent

1. Please rate how effectively you are able to:
   - Discuss the pathophysiology and impact of macrovascular disease on patients with diabetes mellitus
   - Summarize the evidence that intervention with insulin sensitizers, particularly pioglitazone, reduce the incidence of cardiovascular events in patients with diabetes
   - Describe potential mechanisms by which thiazolidinediones are beneficial in the prevention and treatment of macrovascular disease
   - Demonstrate effective cross-disciplinary management of diabetes, including a consideration of macrovascular disease and strategies to improve outcomes

2. Activity/ topic
   - The extent to which this activity met your own continuing professional development goals
   - The overall quality of the activity
   - The overall format of the activity
   - The applicability/usefulness of material to your practice

3. Based on your previous knowledge and experience, the level of this activity was:
   - Too basic □
   - Appropriate □
   - Too complex □

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes □ No □
   If not, explain: __________________________________________

5. How might you change your practice management or patient care on the basis of this activity?

6. Please list any speakers and/or topics you would like to see in future activities.

7. Would a periodic review of this or related material be appropriate? Yes □ No □

8. We welcome your comments. __________________________________________

Thank you for completing the Evaluation Form. Your evaluation of the activity and your comments are important to us and will remain confidential.

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S40  September 2007  THE AMERICAN JOURNAL OF MEDICINE®  Vol 120 (9B)