IMPACT OF CURRENT DIABETES THERAPIES ON MACROVASCULAR OUTCOMES*

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ABSTRACT

Managing diabetes and cardiovascular disease, in addition to improving macrovascular outcomes in people with diabetes, requires attention to the multiple risk factors that contribute to both diseases. Numerous studies have shown that controlling lipids, blood pressure, glucose, and other cardiovascular risk factors associated with insulin resistance reduce the risk for cardiovascular events and death from cardiovascular causes in people with diabetes. This article reviews some of the studies that have demonstrated the cardiovascular benefits of controlling lipids, blood pressure, and glucose, and explains how and why insulin resistance is deleterious to the cardiovascular system. It also discusses interventions to improve insulin sensitivity, with special attention to the benefits of metformin and the glitazones and the importance of redistributing adipose tissue from the viscera to subcutaneous areas outside the abdominal cavity. Recent and ongoing studies in diabetes and prediabetes are also addressed.


NORMALIZING LIPID LEVELS

A better understanding of diabetes, cardiovascular disease, and the strong link between them has changed the approach to the management of both diseases. Instead of focusing primarily on glucose control in diabetes or relieving anginal symptoms in cardiovascular disease, today's approach is to manage the multiple risk factors that contribute to both diseases, particularly those risk factors that are shared by both and/or worsen the prognosis with regard to macrovascular complications.

The underlying premise for this approach is that diabetes itself is a major risk factor for cardiovascular disease. Therefore, earlier detection and appropriate management of diabetes and prediabetes should reduce the risk for cardiovascular events and death from cardiovascular causes. Indeed, numerous studies have shown that controlling lipids, blood pressure, glucose, and other cardiovascular risk factors associated with insulin resistance improves outcomes with regard to macrovascular complications in people with diabetes.

Several landmark studies conducted in the 1990s in subjects with or at risk for coronary heart disease have clearly demonstrated that normalizing lipid levels, particularly total cholesterol and low-density lipoprotein (LDL) cholesterol levels, with statins reduces the risk of cardiovascular events by 25% to 30%. Of special importance was that several of these studies included subjects with diabetes and that the benefits of statin therapy extended to diabetic and nondiabetic subjects alike.

This was confirmed by 2 more recent studies in subjects with diabetes: the Heart Protection Study (HPS), which evaluated simvastatin, and the Treating

*Based on a presentation at a symposium held at the 2006 National Conference of the American Academy of Nurse Practitioners, Grapevine, Texas, on June 24, 2006.
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to New Targets (TNT) study, which evaluated atorvastatin. In the HPS, simvastatin lowered LDL levels by 35 mg/dL versus placebo in all subjects with diabetes, and by 35 mg/dL versus placebo in those with diabetes but no cardiovascular disease. Event rates were 9.4% for simvastatin versus 12.6% for placebo in those patients with diabetes, and 9.3% for simvastatin versus 13.5% for placebo in those with diabetes but no cardiovascular disease. In the TNT study, atorvastatin lowered LDL levels by 22.2% versus placebo, with an event rate of 14.4% in treated subjects versus 18% in those receiving placebo. These findings have convinced many healthcare professionals that all patients with diabetes, particularly type 2 diabetes, should be receiving statin therapy.

Other studies have evaluated the effects of fibrates in normalizing lipids and reducing cardiovascular risk. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial involved more than 2500 men with known coronary heart disease, high-density lipoprotein (HDL) levels less than 40 mg/dL, diabetes (present in 25%), and insulin resistance (50%). The investigators found that gemfibrozil increased HDL by 6% and lowered triglycerides by 31%, but had no significant effect on LDL compared to placebo. After a mean follow-up time of 5.1 years, there was a 22% reduction in cardiovascular events.

By comparison, the Fenofibrate Intervention and Event Lowering in Diabetes study involved nearly 10,000 subjects with type 2 diabetes who were not receiving statins at study entry. Approximately 25% had a history of cardiovascular disease, but the remainder did not. After a placebo and fenofibrate run-in phase, subjects were randomized to fenofibrate or placebo for 5 years. Although fenofibrate reduced the total number of cardiovascular events by 11%, it did not significantly reduce the risk of death from coronary heart disease or the risk of nonfatal myocardial infarction (MI). One explanation for the latter finding is that the higher rate of starting statin therapy in the placebo group may have masked a moderately greater treatment benefit.

**CONTROLLING BLOOD PRESSURE**

Numerous studies have demonstrated that lowering blood pressure markedly reduces the risk of death from cardiovascular causes. In fact, several major hypertension studies have shown that patients with diabetes often derived greater benefit from blood pressure reduction than patients who did not have diabetes. On average, these studies found that a reduction of 10 mm Hg significantly reduced cardiovascular risk.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight control of blood pressure with an angiotensin-converting enzyme inhibitor or a β blocker versus less tight control significantly reduced the risk of microvascular and macrovascular complications in patients with hypertension and type 2 diabetes (Figure 1). Mean blood pressure during follow-up, which extended for a median time of 8.4 years, was significantly reduced from a mean of 160/94 mm Hg at study entry to 144/82 mm Hg in patients assigned to tight control and to 154/87 mm Hg in those assigned to less tight control.

**Figure 1. Impact of Blood Pressure Reduction on Microvascular and Macrovascular Complications**

*From the United Kingdom Prospective Diabetes Study Group (UKPDS 38). Reprinted with permission from United Kingdom Prospective Diabetes Study Group (UKPDS 38), BMJ, 1998;317:703-713.*
**Glucose Control**

Glucose control, through diet and/or glucose-lowering agents, is essential in managing diabetes and reducing the risk of cardiovascular events and macrovascular complications. However, lowering glucose without controlling elevated blood pressure and dyslipidemia will not reduce cardiovascular risk to the extent that it needs to be reduced.

The UKPDS investigated the effects of intensive glucose lowering with a sulfonylurea or insulin versus diet on the risk of microvascular and macrovascular complications in patients with type 2 diabetes. Although the study found that intensive control substantially reduced the risk of microvascular disease, the overall reduction in MI of 16% at 10 years did not reach statistical significance.

However, the Diabetes Control and Complications Trial (DCCT) and its extension, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated an interesting phenomenon with regard to risk for macrovascular complications. In the DCCT, more than 1400 patients with type 1 diabetes—approximately 50% with mild retinopathy—were randomized to intensive therapy (insulin pump or 3 daily injections plus frequent blood glucose monitoring) or conventional therapy (1 or 2 daily injections) and followed for a mean time of 6.5 years for the appearance and progression of retinopathy and other complications. When the DCCT closed in 1993, it was clear that intensive therapy had markedly reduced the risk for microvascular complications by 35% to 90% compared to conventional therapy. Because very few patients in either group had macrovascular complications, there was no significant difference between intensive and conventional therapy in terms of risk reduction.

When the DCCT closed, study patients were followed in the 7-year observational EDIC study; those who had completed conventional therapy and had average glycosylated hemoglobin (HbA1c) levels of approximately 9% (vs 7.3% in those receiving intensive therapy) were encouraged to switch to intensive treatment. They were taught intensive management techniques, referred back to their primary care health providers, endocrinologists, or whoever was managing their care, and monitored extensively over the next 7 years. After approximately 1 year, HbA1c levels in patients initially randomized to intensive therapy and in those who had switched from conventional therapy averaged approximately 8%, where they remained for the rest of the EDIC study.

What emerged over the course of the EDIC study was that the longer patients remained in the study, the greater their reduction in risk for macrovascular complications. In the most recently published EDIC report, patients initially randomized to intensive therapy had a 57% reduction in macrovascular events compared to those initially randomized to conventional therapy even though average HbA1c levels were essentially identical in both groups for the previous 7 years.

Although the EDIC findings suggest that the risk reductions conferred by intensive glucose therapy in the DCCT persist over time, the findings also suggest that better glucose control is still needed to reduce the risk of macrovascular complications to the lowest possible level.

**Multifactorial Intervention**

The first study to investigate the effects of multiple risk factor intervention on microvascular and macrovascular complications was Steno-2, so called because it studied patients with type 2 diabetes and was conducted by investigators at the Steno Diabetes Center in Copenhagen, Denmark. The study involved 160 patients who were at high risk for cardiovascular events because of albuminuria. Mean characteristics at baseline were: age, 55 years; body mass index (BMI), 30; duration of diabetes, approximately 5.8 years; and A1c level, 8.6%. Patients were randomized to conventional therapy (n = 80), which followed Danish national guidelines, or intensive therapy (n = 80), which was the stepwise implementation of behavioral modification; pharmacologic therapy to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria; and daily aspirin for the secondary prevention of cardiovascular disease. Patients were then followed for a mean time of 7.8 years.

At the end of the study, patients who received intensive therapy had lowered their A1c levels from 8.6% to approximately 7.8%, which was an improvement, but higher than the study goal of less than 6.5%. Their systolic blood pressure (132 mm Hg), LDL cholesterol (75 mg/dL), and triglyceride levels (150 mg/dL) were well controlled. By comparison, those patients who received conventional therapy demonstrated a rise in A1c to approximately 9% and
poor control of systolic blood pressure (148 mm Hg), LDL (130 mg/dL), and triglycerides (260 mg/dL).

The primary endpoint of Steno-2 was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, or amputation. Whereas 55% of patients receiving conventional therapy suffered 1 or more of these macrovascular events by study's end, those receiving intensive therapy had a 53% reduction in risk for these events (Figure 2). The study thus demonstrates that intensive therapy of multiple risk factors is highly effective in reducing risk for cardiovascular events and that better glucose and blood pressure control should reduce risk even further.

Both the American Diabetes Association and American Heart Association have recommended target levels for the major cardiovascular risk factors: LDL less than 100 mg/dL in patients with diabetes and less than 70 mg/dL in patients with diabetes and established vascular disease, including kidney disease; blood pressure lower than 130/80 mm Hg; and $A_1C$ less than 7%. The American Association of Clinical Endocrinologists has recommended $A_1C$ less than 6.5%.

**OTHER CARDIOVASCULAR RISK FACTORS**

Other risk factors for cardiovascular disease that require intervention in patients with diabetes include overweight/obesity, smoking, sedentary lifestyle, endothelial dysfunction and inflammation, and coagulation, and insulin resistance.

**INSULIN RESISTANCE**

Insulin resistance is associated with multiple traditional and nontraditional risk factors for cardiovascular disease. These risk factors include type 2 diabetes and glycemic disorders, such as impaired glucose tolerance or impaired fasting glucose, dyslipidemia, hypertension, endothelial dysfunction and inflammation, and impaired thrombosis. All are involved in the development of atherosclerosis.

Many, but not all, insulin-resistant patients have an increased waist circumference. However, although increased waist circumference and BMI strongly suggest insulin resistance, they are not diagnostic. What really matters is how much fat is within the viscera as opposed to how much fat is outside the abdominal cavity. A ratio of visceral to subcutaneous fat of more than 0.4 indicates high risk for the metabolic complications of insulin resistance. As shown in Figure 3, individuals with a normal BMI can have differing amounts of visceral and subcutaneous fat, divergent visceral to subcutaneous fat ratios, and dissimilar risks for insulin resistance. The areas of visceral and subcutaneous fat shown in the panel on the left yield a ratio of 1.27 (146 divided by 115) and a high risk for the complications of insulin resistance, whereas the areas of visceral and subcutaneous fat shown in the panel on the right yield a ratio of 0.32 (60 divided by 190) and a lower risk.

The “overflow” hypothesis holds that adipocytes represent a storage depot for energy (ie, fat). When the capacity of these cells to store fat in the subcutaneous tissues is outstripped by excessive food intake, the excess fat overflows into muscle, where it causes resistance to the action of insulin; into the liver, where it promotes hepatic gluconeogenesis; and into the pancreas, where it is associated with decreased insulin secretion.

![Figure 2. Multifactorial Intervention for Type 2 Diabetes *](image-url)
Adipocytes produce several different proteins, known collectively as adipocytokines, that profoundly influence insulin sensitivity and glucose metabolism and are involved in insulin resistance, \( \beta \)-cell dysfunction, and endothelial dysfunction and inflammation.\(^{12,13}\) These proteins include angiotensin II; leptin; resistin, which is closely associated with insulin resistance; C-reactive protein (CRP), an inflammatory mediator; adiponectin, which promotes insulin sensitivity; free fatty acids, which eventually become triglycerides; plasminogen-activator inhibitor-1 (PAI-1), which increases blood clotting; and tumor necrosis factor-\( \alpha \) and interleukin-6, both of which are pro-inflammatory cytokines. As discussed in greater detail later in this article, several of these proteins can be favorably altered by pharmacologic and nonpharmacologic interventions.

**IMPROVING INSULIN SENSITIVITY**

Improving insulin sensitivity is instrumental in the management of diabetes and in the prevention of progression from prediabetes to diabetes. Insulin resistance is reduced by weight loss—through calorie and fat restriction and increased exercise—and/or medications, primarily metformin and the glitazones.

**Metformin.** Metformin is a modest insulin sensitizer that acts primarily on the liver to decrease hepatic glucose output. As such, it lowers A1C levels by 1% to 2%.\(^{14}\)

Metformin also has favorable effects on lipids, blood pressure, microalbuminuria, CRP, PAI-1, vascular reactivity, and endothelial function. For example, metformin decreases LDL levels by 5% to 10% and triglyceride levels by 15%.\(^{14}\)

In a UKPDS substudy of obese patients who participated in a large study comparing intensive versus conventional glucose control, metformin plus diet was associated with a 32% reduction in any diabetes-related event and a 39% reduction in MI.\(^{15}\) Inexplicably, the substudy also found that combination therapy with metformin and a sulfonylurea increased diabetes-related mortality, thus this requires further investigation.

**Glitazones.** Thiazolidinediones (TZDs), or glitazones, work through the peroxisome proliferator-activated receptor \( \gamma \) (PPAR\( \gamma \)) system, which is abundant in adipose tissue and thought to be a “master switch” in adipogenesis, lipid metabolism, and glucose control. PPAR\( \gamma \) interacts with a ligand and recruits the retinoid X receptor as a coactivator. Together, they form a dimer and work at the gene level to promote transcription. The resulting protein transcription product favorably affects fat cells, lipid metabolism, insulin sensitivity, and blood vessel walls. As shown in Figure 4, PPAR\( \gamma \) activation helps redistribute fat from the visceras to outside the abdominal cavity and just underneath the skin.

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**Figure 3. Visceral Versus Subcutaneous Fat**

Excess visceral fat = visceral fat area ≥ 130 cm

**Figure 4. Effect of PPAR\( \gamma \) Activation on Redistribution of Abdominal Fat**

Before | After
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Visceral Fat | Subcutaneous Fat
BMI: 23.1 kg/m \(^2\) | BMI: 24.0 kg/m \(^2\)

BMI = body mass index. Reprinted with permission from Wajchenberg, Endocr Rev. 2000;21:697-738.\(^{11}\)
A study examining the effect of pioglitazone on abdominal fat distribution found a 10% reduction in the visceral fat area, a 15% increase in the subcutaneous fat area, and a marked improvement in the visceral to subcutaneous fat ratio, which was reduced from 0.59 to 0.44. A study comparing rosiglitazone to metformin in patients with increased hepatic fat found that the glitazone reduced the amount of fat in the liver by 51% (vs a slight increase in fat in the metformin-treated group). This finding is significant because there is a growing body of evidence suggesting that intrahepatic fat may be one of the earliest changes that occur in patients with metabolic syndrome or insulin resistance.

Peroxisome proliferator-activated receptor γ activation by a glitazone reduces visceral fat and increases subcutaneous fat, resulting in less resistance to insulin action in the liver, muscle, and adipose tissue. This, in turn, leads to decreased glucose production, increased glucose uptake, and improved β-cell secretion in the pancreas. The net result is less vascular inflammation, a cardiovascular benefit. Other cardiovascular benefits of PPARγ activation by glitazones include normalization of lipid levels, blood pressure reduction, decreased levels of PAI-1 and CRP, reduced endothelial cell dysfunction, increased levels of adiponectin, reduced proliferation and migration of vascular smooth muscle cells in the arterial wall, reduced excretion of microalbumin, and a decrease in carotid intimal medial thickness.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was specifically designed to evaluate the effects of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease. More than 5200 patients were recruited and assigned to pioglitazone or placebo, both to be taken in addition to their usual glucose-lowering drugs and other medications. The primary endpoint was the composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The secondary endpoint was the composite of all-cause mortality, nonfatal MI, and stroke.

As shown in the Table, there were highly significant differences between the treatment and placebo groups with regard to A1c, triglycerides, LDL, HDL, and LDL/HDL from baseline to the last visit. Most of the differences favored treatment with pioglitazone. Although there was a 10% reduction in risk in the treatment group for the primary composite endpoint, the difference was not statistically significant. Nevertheless, there was a statistically significant 16% reduction in the predefined secondary composite endpoint of stroke, MI, and all-cause mortality in the treatment group. However, there was an increased risk of heart failure in patients receiving pioglitazone, but no significantly increased risk of hospitalization for heart failure or fatal heart failure.

It has been suggested that the significant 16% reduction in stroke, MI, and all-cause mortality in the PROactive study reflects the effects of pioglitazone on A1c, triglycerides, and HDL rather than its impact on insulin resistance. Many also think that the study population, with macrovascular disease already present, may not have been able to benefit from TZD/glitazone therapy because they were too far advanced in the spectrum of disease. Therefore, the possibility of greater benefit with glitazones in primary prevention cannot be ruled out.

Current data suggest that TZDs provide intrinsic vascular benefit in patients with diabetes. Ongoing studies examining the effects of these agents in preventing diabetes and its vascular complications should provide definitive answers before the end of 2009.

| Table. Mean Change in Glucose and Lipid Values from Baseline to Final Visit in the PROactive Study |
|---------------------------------|-----------------|---------------|
|                                 | Pioglitazone    | Placebo       | P Value     |
| Glycosylated hemoglobin (change)| -0.8%           | -0.3%         | <.0001      |
| Triglycerides                   | -1.14%          | 1.8%          | <.0001      |
| LDL                             | 7.2%            | 4.9%          | <.003       |
| HDL                             | 19.0%           | 0.1%          | <.0001      |
| LD/LHDL                         | -9.5%           | -4.2%         | <.0001      |

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events.
CONCLUSIONS

Managing diabetes requires more than glucose control. Because diabetes and cardiovascular disease share several risk factors, and because diabetes itself is a major risk factor for cardiovascular disease, the management approach should target multiple risk factors. Lifestyle modifications, such as weight loss, exercise, and smoking cessation, are the first step in reducing risk. If they are not sufficient in normalizing lipid levels, pharmacologic therapy should be implemented, as necessary, to aggressively control blood pressure, hyperglycemia, and hyperlipidemia.

Studies have shown that drug therapy to normalize lipids and lower blood pressure reduces the risk for cardiovascular events. Other studies have shown that intensive drug therapy to control glucose is superior to conventional therapy in reducing the risk of microvascular and macrovascular complications. The Steno-2 study, in particular, demonstrated the benefits of multiple risk factor intervention.

Insulin resistance, which heralds prediabetes and is present in most patients with type 2 diabetes, is associated with several risk factors for cardiovascular disease. It is also associated with excess visceral fat in most patients. Interventions to reduce insulin resistance and increase insulin sensitivity include weight loss through diet and exercise and/or with medications, primarily metformin and the glitazones. Results of ongoing studies examining the effects of the latter in preventing diabetes and its vascular complications are expected later this year and through 2009.

REFERENCES