# Health Outcomes Beyond Glucose Control

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***Abstract***

Direct and indirect costs for diabetes mellitus place a large economic burden on the US healthcare system. Diabetes and cardiovascular disease (CVD) are closely interrelated, and it is estimated that much of the burden of CVD too is attributable to diabetes. Insulin resistance may be the common link between diabetes and CVD, often manifested clinically as the metabolic syndrome. The thiazolidinediones (TZDs) reduce insulin resistance and have favorable effects on lipids, blood pressure, and other cardiovascular risk factors. Large clinical trials have shown that early, aggressive intervention with lifestyle changes and pharmacotherapy with TZDs and other agents may slow progression to overt diabetes in high-risk patients and reduce the risk of cardiovascular and other complications; this could reduce healthcare resource utilization and costs.

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Diabetes mellitus imposes a huge economic burden. In 2003, the American Diabetes Association (ADA) estimated that direct and indirect costs of types 1 and 2 diabetes in the United States totaled $132 billion.[1] Direct medical expenditures for 12.1 million US residents with diabetes were $91.8 billion, including $23.2 billion for diabetes care, $24.6 billion for chronic complications, and $44.1 billion for excess prevalence of general medical conditions. Per capita total healthcare expenditures were $13 243 for persons with diabetes versus $2560 for those without diabetes. Total analyzed healthcare costs for persons with diabetes were almost one fifth of the cost of the entire US population ($160 billion vs $865 billion, respectively). Indirect costs of lost productivity, measured in lost work days, restricted activity days, premature mortality, and permanent disability, totaled $39.8 billion.[1]

Up to one third of people with diabetes remain undiagnosed, and the cost estimates did not include undiagnosed cases.[1] Costs of unpaid caregivers and expenditures for health services used more by persons with diabetes (eg, optometry, licensed dietitians) were not included. Therefore, total costs were probably underestimated in the study. Based on current prevalence rates and population estimates, the burden of diabetes could rise from the estimated $132 billion to $156 billion by 2010.[1] If prevalence rates increase due to rising levels of obesity, the costs could be higher still.

The inpatient, outpatient, and pharmacy costs of diabetes are strongly related to glycemic control.[2] In a study of 28 335 Kaiser Permanente members, rising fasting plasma glucose (FPG) levels corresponded to rising healthcare costs.[2] This would suggest that treatment resulting in tight glycemic control has the potential to lower costs.

A study of patients with diabetes whose health maintenance organizations sponsored disease management programs demonstrated that effective treatment can lower costs.[3] Compared with nonprogram patients, the patients enrolled in disease management received more preventive care. Larger proportions of patients received testing for glycated hemoglobin (A1C) levels and lipids, kidney screening, and eye screening, and a smaller proportion had A1C levels >9.5%. Program patients had fewer emergency department visits and fewer and shorter hospital admissions. Overall, the costs of patients in diabetes disease management were significantly lower at $1294.32 less per patient per year (**Table**). Patients who chose to enroll in disease management might have had better adherence and better health practices; however, the results demonstrate clearly the cost advantage of making disease management programs available.[3]

Diabetes is not receiving the research funding it deserves in the United States.[2] Compared with the ADA 2003 cost estimate of $132 billion, the 2003 National Institutes of Health (NIH) funding for diabetes research was $910 million, or less than 1%, not enough for a public health issue of this magnitude. NIH expenditures rose slightly in fiscal years 2004 and 2005, but then flattened at $1.055 billion in the 2006 fiscal year.[4] The 2007 fiscal year budgetary request decreased by $2 million from the 2006 fiscal year.[4] The 2007 fiscal year budget request for the National Institute of Diabetes and Digestive and Kidney Diseases decreased by $410.6 million from the 2006 fiscal year.[5] Thus, while diabetes prevalence is increasing, government research funding is decreasing, a disheartening situation for healthcare professionals and all Americans affected by the disease.

**Table.** Type 2 Diabetes Disease Management Programs: Costs

| | Program | Nonprogram |
|---|---|---|
| Demographic | 3118 | 3681 |
| Mean member per month paid charges | $394.62 | $502.48 |
| A1C testing (%) | 3019 (96.6) | 3083 (83.8) |
| A1C, uncontrolled (%) | 35 (6.7) | 79 (14.4) |
| Lipid testing (%) | 2840 (91.1) | 2856 (77.6) |
| Kidney screening (%) | 2135 (68.5) | 1446 (39.3) |
| Eye screening (%) | 2469 (79.1) | 2388 (64.9) |

A1C indicates glycated hemoglobin.
*Source:* Reference 3.

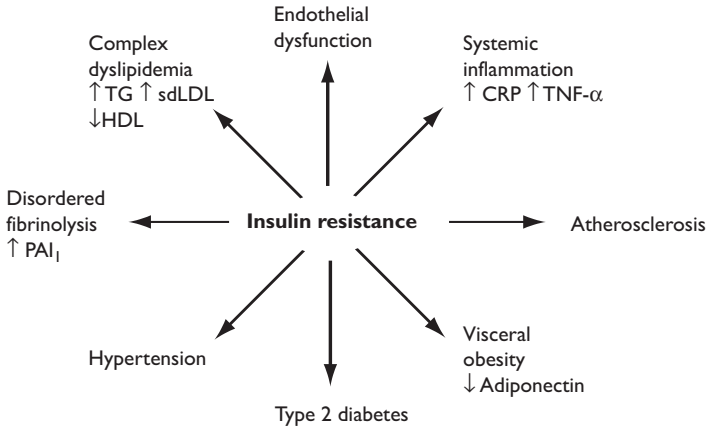
### Diabetes, Cardiovascular Disease, and the Metabolic Syndrome

According to the ADA, much of the burden of cardiovascular disease (CVD) is attributable to diabetes.[1] Utilization attributable to diabetes includes 16% to 20% of healthcare visits for CVD, 19% of inpatient days with a primary diagnosis related to CVD, and 19% of deaths with CVD listed as the primary cause.[1] Coronary heart disease is the leading cause of death in persons with diabetes.[1,6]

Insulin resistance, a primary risk factor for and feature of diabetes, may be the common link between diabetes and CVD.[7] The relationship is often manifested clinically in the metabolic syndrome.[8-10] In 1988, Reaven proposed that insulin resistance and compensatory hyperinsulinemia were also involved in the pathogenesis of coronary artery disease (CAD).[11] He suggested that hyperinsulinemia, hypertension, glucose intolerance, increased triglyceride concentrations, and decreased high-density lipoprotein (HDL) cholesterol were secondary to insulin resistance, and called the cluster of risk factors "Syndrome X."[11] The constellation of CVD risk factors linked to insulin insensitivity has since become known as the insulin resistance syndrome or, more commonly, the metabolic syndrome. In metabolic syndrome, insulin resistance contributes to hypertension, complex dyslipidemia marked by decreased HDL cholesterol and increased triglycerides and small, dense low-density lipoprotein (LDL) cholesterol particles, disordered fibrinolysis marked by elevated plasminogen activator inhibitor, and endothelial dysfunction, leading to atherosclerosis.[8-10,12] Systemic inflammation marked by elevated levels of C-reactive protein (CRP) and tumor necrosis factor-alpha, and visceral obesity marked by decreased levels of vasoprotective adipocytes, such as adinopectin, aggravate and are aggravated by insulin resistance (**Figure 1**).[7,10,12] The National Cholesterol Education Program Adult Treatment Panel III set diagnostic criteria for metabolic syndrome as 3 or more of the following: blood pressure (BP) ≥130/≥85 mm Hg, FPG ≥110 mg/dL, triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, and waist circumference >40 inches in men or >35 inches in women.[9,13] Studies have shown that patients diagnosed with metabolic syndrome have 30% to 400% higher CVD risk than those without it.[12] Metabolic syndrome with diabetes increases the high risk for cardiovascular complications inherent in uncontrolled diabetes.[9,13]

Recently, some diabetes experts have raised doubts about the value of focusing on the metabolic syndrome (as defined above) as a principal CVD risk marker.[12] In a joint statement, the ADA and the European Association for the Study of Diabetes noted that definitions of metabolic syndrome are imprecise

**Figure 1.** The Metabolic Syndrome of Insulin Resistance




TG indicates triglyceride; sdLDL, small, dense low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; TNF-α, tumor necrosis factor-alpha; $PAI_1$, plasminogen activator inhibitor-1.
*Sources:* References 8, 10.

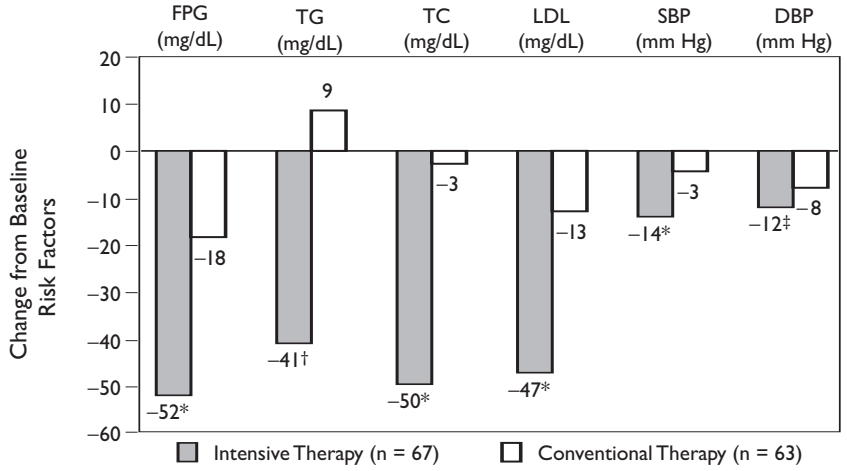
and inconsistent.[12] The associations recommended that clinicians should evaluate adults presenting with any major CVD risk factor for other CVD risk factors. They recommended that all CVD risk factors (including type 2 diabetes) be treated individually, regardless of whether a patient meets diagnostic criteria for metabolic syndrome. Thus patients with risk factors should be counseled on lifestyle changes and, if reaching disease cut points, should be treated according to established guidelines.[12]

The Steno-2 study demonstrated the benefits of using an early, aggressive, multifactorial approach to CVD prevention in patients with risk factors including type 2 diabetes and microalbuminuria.[14] Patients newly diagnosed with diabetes were randomized to an intensive intervention of behavior modification and pharmacologic therapy or conventional therapy from their general practitioner. Compared with the conventional therapy patients, the intensive therapy patients achieved significantly greater reductions in BP, FPG, A1C, triglycerides, and total and LDL cholesterol levels (**Figure 2**).[14] At 96 months, cardiovascular risk was reduced in the intensive therapy group by approximately 50% (**Figure 3**).[14]

### Cardiovascular Effects of Thiazolidinediones

The renewed focus on multifactorial risk reduction has given some legitimacy to the use of polypharmacy to prevent CVD. In this

**Figure 2.** Steno-2 Study: Changes in Risk Factors at 7.8 Years



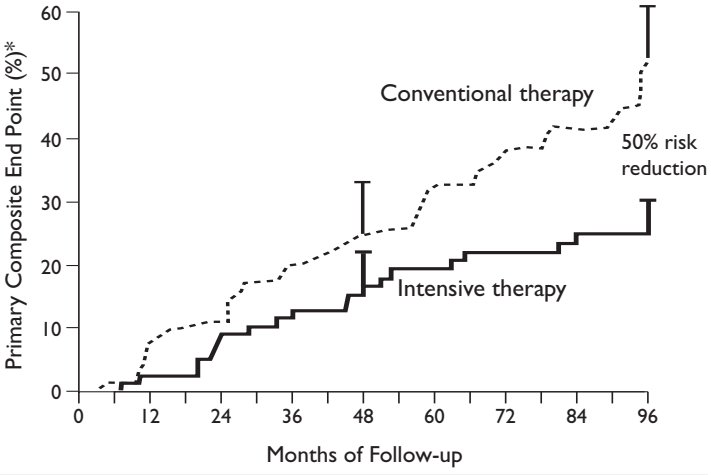

*$P$ <.001; †$P$ = .015; ‡$P$ = .006.
Intensive therapy = strict treatment goals and stepwise implementation of behavior modification and targeted pharmacologic therapy overseen by project team; conventional therapy = treatment from general practitioner according to Danish Medical Association guidelines.
FPG indicates fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*Source:* Reference 14.

context, interest has risen in the use of drugs, such as the thiazolidinediones (TZDs), that may have multiple beneficial effects on atherosclerosis progression in addition to their ability to lower blood glucose.[7,15-36] TZDs have been shown to improve lipid profiles,[15,16] BP,[15,16] insulin sensitivity, and beta cell function, as estimated by homeostasis model assessment (HOMA) indices,[17-25] the inflammatory markers CRP[15,17,24,26] and fibrinogen,[15,24] free fatty acids,[15-17,22,23,26-28] homocysteine levels,[19] and the thrombotic risk marker plasminogen activator inhibitor-1.[15,16,18] Some evidence suggests better effects on LDL cholesterol, total cholesterol, and triglyceride levels with pioglitazone than rosiglitazone.[19,20,27,29-32] Both TZDs can significantly improve HDL cholesterol concentrations[27,28,30,33,34] and LDL cholesterol particle size.[15,16,28,30,34] The antiatherogenic effects of TZDs may derive from their activation of the nuclear transcription factor peroxisome proliferator-activated receptor-γ in vascular cells, thereby inhibiting vascular smooth muscle cell proliferation, endothelial cell activation, and inflammation within the vessel wall.[24-26,35]

In-stent restenosis after coronary stent implantation occurs more frequently in patients with diabetes.[37] In a study of patients with type 2 diabetes and CAD, Choi and associates added rosiglitazone to conventional antidiabetic therapy 1 day before patients underwent coronary stent implantation.[26] After the procedure and 6 subsequent months of treatment, the rosiglitazone-treated patients had a significantly reduced rate of restenosis and a significantly lower degree of diameter stenosis compared with controls treated with conventional antidiabetic therapy only (**Figure 4**).[26] In another trial following patients with diabetes after stent implantation, restenosis occurred less frequently and an index of neointimal tissue proliferation was significantly smaller with pioglitazone treatment.[37] The reduction in restenosis with TZDs could potentially mean reduced future CVD-related costs.

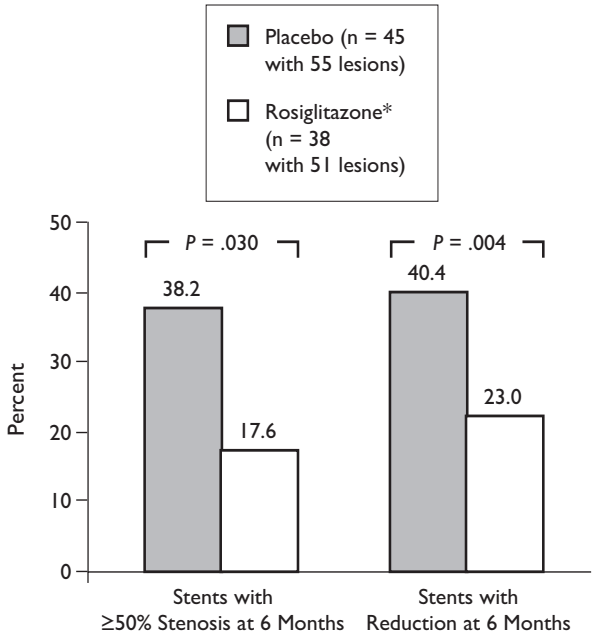
Several studies have shown a reduction in carotid atherosclerosis with TZDs.[7,25,35,36] Minamikawa and associates gave troglitazone to patients with type 2 diabetes for 6

**Figure 3.** Steno-2: Composite End Point




*P* = .007.
*Death due to CV causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease in the conventional-therapy group and the intensive-therapy group.
CV indicates cardiovascular.
Adapted from Reference 14.

**Figure 4.** Preventive Effects of Rosiglitazone on Restenosis in Patients With Type 2 Diabetes




*Rosiglitazone initiated with 8 mg before undergoing catheterization and 4 mg daily thereafter, combined with conventional antidiabetic therapy.
*Source:* Reference 26.

months in addition to their usual sulfonylurea (SU) or diet management. The patients taking troglitazone showed a significant decrease in carotid artery intimal medial thickness (IMT), a surrogate marker of atherosclerotic disease progression. In contrast, the IMT of controls treated with diet only or SUs increased.[36] In a second similar study by the same research group, patients who received pioglitazone had a significant decrease in IMT.[35]

Sidhu and associates assessed the effect of rosiglitazone on carotid IMT in patients with CAD but without diabetes.[25] After 48 weeks of rosiglitazone or placebo treatment, the patients taking rosiglitazone had significantly reduced IMT progression. Because insulin resistance also declined in the TZD-treated patients, the authors concluded that insulin sensitization may contribute to reduced IMT progression.[25]

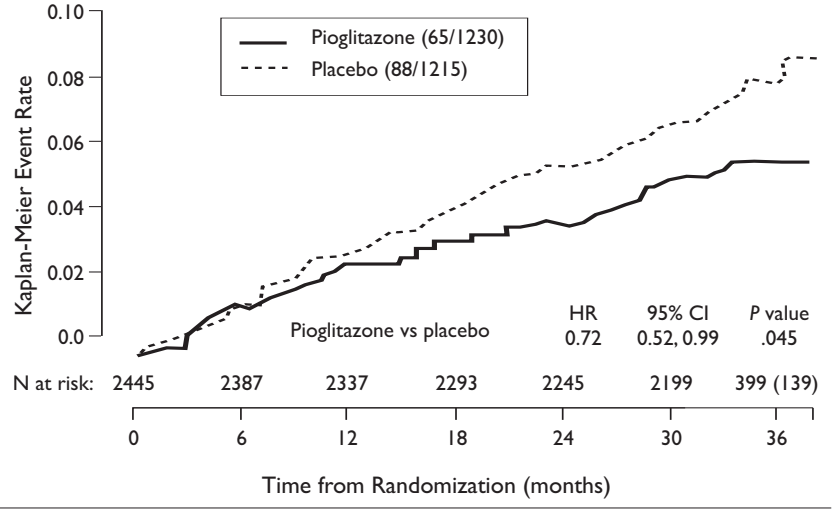
Finally, a 24-week trial of patients with type 2 diabetes confirmed that the antiatherogenic effect of a TZD (pioglitazone) was not dependent on glycemic control.[7] A1C improved similarly with pioglitazone and the SU glimepiride, but improvements in carotid IMT and HOMA occurred only in the pioglitazone group. The IMT reductions correlated with reductions in measures of insulin resistance and were independent of glycemic control improvements.[7]

The multicenter PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) addressed the issue of whether TZDs reduce CVD events in a cohort of diabetic patients already at high risk for these events.[33,38] Patients with type 2 diabetes and macrovascular disease were randomized to add pioglitazone or placebo to their other glucose-lowering medications for a trial duration of 4 years.[33,38] Although differences in the primary end point results did not reach statistical significance, the patients taking pioglitazone had a 16% relative risk reduction in the secondary end point of all-cause mortality, nonfatal myocardial infarction (MI), and stroke compared with the placebo group.[33] For a subgroup of patients with a previous MI, treatment with pioglitazone significantly reduced the risk of a recurrent fatal or nonfatal MI by 28% and the risk of acute coronary syndrome by 37% (**Figure 5**).[33] An editorial commentary and several letters raised questions about the lack of significance for the primary end point, the post hoc use of a main secondary end point, and the increased incidence of heart failure (HF); the authors responded that there was no difference in mortality from HF and some cases of HF were probably misdiagnosed.[39-45]

An ongoing multinational trial will specifically address insulin sensitization for CVD protection in patients with diabetes.[46] The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial will assess 5-year mortality of patients with type 2 diabetes and stable CAD whose glycemic control is accomplished by an insulin-sensitizing strategy (eg, TZDs) versus an insulin-providing strategy (eg, SUs, insulin analogs). The treatment phase is expected to end in mid-2007.[46]

To summarize, clinical data suggest that TZDs have a beneficial effect on the pathophysiology of atherosclerosis. Potential outcome

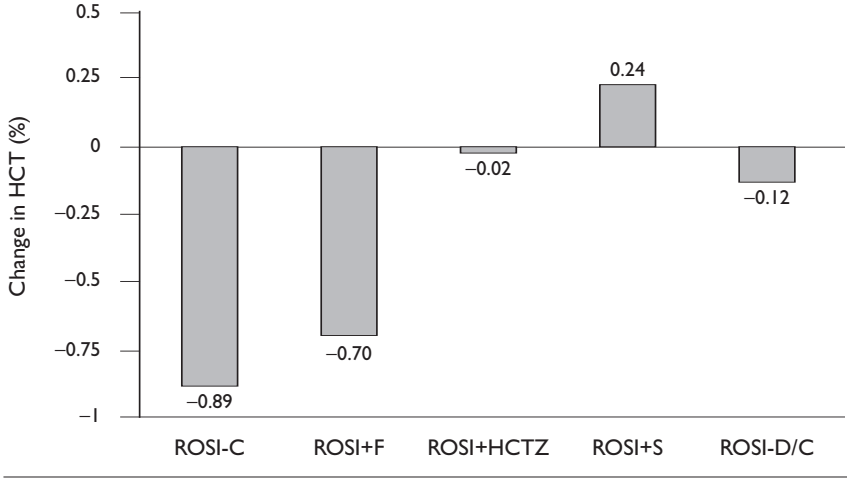
**Figure 5.** Time to Fatal/nonfatal MI (excluding silent MI)




MI indicates myocardial infarction; HR, hazard ratio; CI, confidence interval.
The official PROspective Actos Clinical Trial In macroVascular Events (PROactive) results Web site. Available at: http://www.proactive-results.com/html/analysis.htm. Accessed January 12, 2006.

benefits of these effects have been demonstrated by the significant reduction of restenosis after coronary angioplasty. Large, prospective outcome studies that investigate the effect of TZDs on cardiovascular events are currently under way.[15]

**Figure 6.** Managing TZD-related Fluid Retention by Various Treatment Options




TZD indicates thiazolidinedione; HCT, hydrochlorothiazide; ROSI-C, continue rosiglitazone; ROSI+F, rosiglitazone plus furosemide; ROSI+S, rosiglitazone plus spironolactone; ROSI-D/C, discontinue rosiglitazone.
*Source:* Reference 52.

### Clinical Management Issues With TZDs

Weight gain, common with oral antidiabetic agents, can be a concern for patients whose obesity contributes to overall cardiovascular risk. As noted elsewhere in this supplement, weight gain from TZDs appears to occur preferentially in peripheral adipose tissues rather than in visceral adipose depots.[23,47,48] Weight gain from TZDs may also result partly from fluid retention.

The average weight gain with a monotherapy SU is ~1.8 kg, with a non-SU secretagogue of ~1.0 to 1.6 kg, a TZD of ~0.5 to 3.0 kg, and combination therapy of TZD plus SU of 1.9 to 2.9 kg.[47,49,50] With metformin alone, weight change can range from a loss of 0.6 kg to a gain of 3.8 kg. Metformin combination therapies can minimize weight gain. Adding metformin to SU therapy decreases the average weight gain to 0.9 kg, and adding metformin to TZD therapy decreases the gain to 1.0 kg.[47,49,50]

Behavioral weight management programs can be beneficial when using oral antidiabetic agents.[48] In a case series of obese patients with type 2 diabetes, treatment including rosiglitazone (n = 2) or pioglitazone (n = 6) resulted in decreased mean A1C and improvement in mean systolic and diastolic BP. All patients participated in a low-calorie diet, and all lost weight in 12 weeks and maintained the loss for at least 1 year. Their mean weight decreased from 270 ± 54 lb to 244 ± 61 lb ($P$ <.01), a weight loss comparable with that of 16 matched controls in the diet program who were not receiving TZDs. The investigators concluded that patients being treated with TZDs can lose weight with a program of caloric restriction and behavior modification.[48]

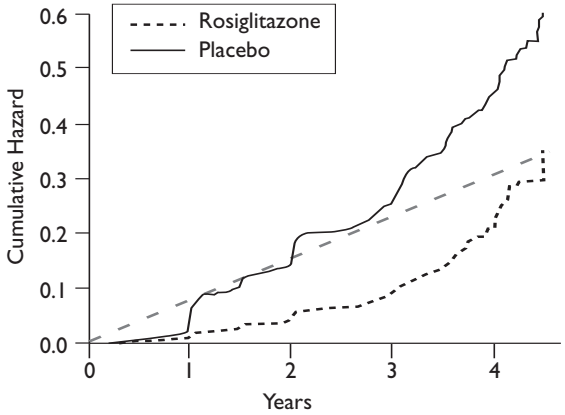
Fluid retention caused by plasma volume expansion, a common effect of TZDs, can increase the risk for congestive heart failure (CHF) in vulnerable patients,[51] but can be managed with proper monitoring and treatment.[52] Karalliedde and associates studied TZD use in 381 patients receiving SU monotherapy or SU plus metformin. Rosiglitazone was added for all patients for 12 weeks. Those who experienced volume expansion (as assessed by hematocrit reduction ≥0.5%) were then randomly assigned to the following groups:

ROSI-C: Continue rosiglitazone
ROSI+F: Add furosemide 40 mg/day
ROSI+HCTZ: Add hydrochlorothiazide 25 mg/day
ROSI+S: Add spironolactone 50 mg/day
ROSI-D/C: Discontinue rosiglitazone.

After 7 days, hematocrit continued to decrease in the ROSI-C and ROSI+F groups. The ROSI+S group showed a hematocrit increase, suggesting that spironolactone was most effective in treating fluid retention associated with rosiglitazone use (**Figure 6**).[52]

The American Heart Association and ADA have published a consensus statement on

**Figure 7.** DREAM: Time to Occurrence of Primary Outcome




**Number at risk**

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 2634 | 2470 | 2150 | 1148 | 177 |
| Rosiglitazone | 2635 | 2538 | 2414 | 1310 | 217 |

Reproduced from Reference 55.

the use of TZDs in the context of the risk of precipitating CHF.[51] The statement notes that TZDs alone, or particularly in combination with exogenous insulin, may cause fluid retention, which can lead to HF. The incidence of CHF, <1% with TZD monotherapy, can rise to 2% to 3% for combined therapy with TZDs and insulin.[51,53] An edema incidence of 14.7% has been reported in trials of TZDs and insulin combination therapy.[53] Therefore TZDs are not recommended for patients with New York Heart Association class III or IV HF. All patients should be observed for signs and symptoms of HF, and TZDs should be discontinued if any deterioration in cardiac status occurs.[51]

### Early Intervention in Diabetes

Current trials are demonstrating the benefits of early aggressive intervention in type 2 diabetes. TZDs remain an important treatment option. The multicenter Rosiglitazone Early vs SULphonylurea Titration (RESULT) study assessed the value of adding rosiglitazone to SU therapy instead of first increasing the SU dosage.[23,54] Patients with type 2 diabetes were randomized to glipizide plus rosiglitazone or glipizide plus placebo.[23] Disease progression (FPG ≥10 mmol/L) was reported in 2% of patients receiving rosiglitazone versus 28.7% of patients receiving glipizide monotherapy. The combination therapy resulted in significantly improved A1C, FPG, free fatty acids, and HOMA-IR.[23] The patients receiving rosiglitazone had greater treatment satisfaction and higher quality-of-life scores, significantly fewer emergency department visits, and significantly fewer and shorter inpatient hospital stays.[23] A cost analysis of the same trial showed that costs per patient per month were significantly lower in the rosiglitazone group,[54] suggesting again that more effective treatment can reduce costs.

The multinational Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial measured outcomes after intervention early in the progression of insulin resistance, before the development of frank diabetes in adults at high risk for diabetes. The investigators followed 5269 patients with impaired fasting glucose, impaired glucose tolerance, or both for a median of 3 years.[55] Patients were randomized to the angiotensin-converting enzyme (ACE) inhibitor ramipril or placebo and rosiglitazone or placebo. The primary outcome was development of type 2 diabetes or death. Secondary outcomes included cardiovascular or renal events; changes in other glycemic, cardiovascular, and renal measures; beta cell function; insulin resistance; and reversion to normal glucose tolerance. The study was controlled for the use of other ACE inhibitors and antidiabetic agents.

The results suggested that addition of rosiglitazone to lifestyle changes substantially reduces the risk of developing diabetes by about two thirds and increases the likelihood of return to normoglycemia in high-risk individuals. The primary outcome of death or diabetes occurred in 60% fewer patients (11.6%) in the rosiglitazone group than in the placebo group (26.0%) ($P$ <.0001) (**Figure 7**). In addition, patients who received rosiglitazone were 70% to 80% more likely to return to normal blood glucose levels compared with those who received placebo ($P$ <.0001). Cardiovascular event rates were similar in the 2 groups, although there was a small excess in nonfatal CHF in rosiglitazone recipients.[55]

A second double-blind, multinational trial, A Diabetes Outcome Progression Trial (ADOPT), will compare the effects of 3 treatments with differing mechanisms of action.[56]

Patients whose diabetes has been managed only with diet and exercise will be randomized to receive glyburide, metformin, or rosiglitazone and followed for 4 years; the primary outcome will be time to treatment failure. Secondary outcomes will include insulin sensitivity, beta cell function, dyslipidemia, and other cardiovascular changes. Based in part on the conclusions of the United Kingdom Prospective Diabetes Study that beta cell function declines progressively despite monotherapy with insulin, sulfonylureas, or metformin,[57] the investigators expect 25% of the glyburide and metformin groups to reach monotherapy failure within 4 years compared with 18.2% of the rosiglitazone group.[56]

## Conclusions

Multi-interventional therapies, including behavior modification and medications, are effective for patients with type 2 diabetes. Therapy combining oral medications with complementary modes of action can be more effective than monotherapy and have fewer adverse effects. Early aggressive treatment of diabetes while beta cells still function can forestall disease progression and prevent micro- and macrovascular complications. Tight glycemic control is cost effective over the long term because it reduces resource utilization. TZDs address the insulin resistance components of diabetes while reducing cardiovascular risk. Ongoing outcome studies will confirm that TZDs have anti-inflammatory effects on the vasculature.

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