

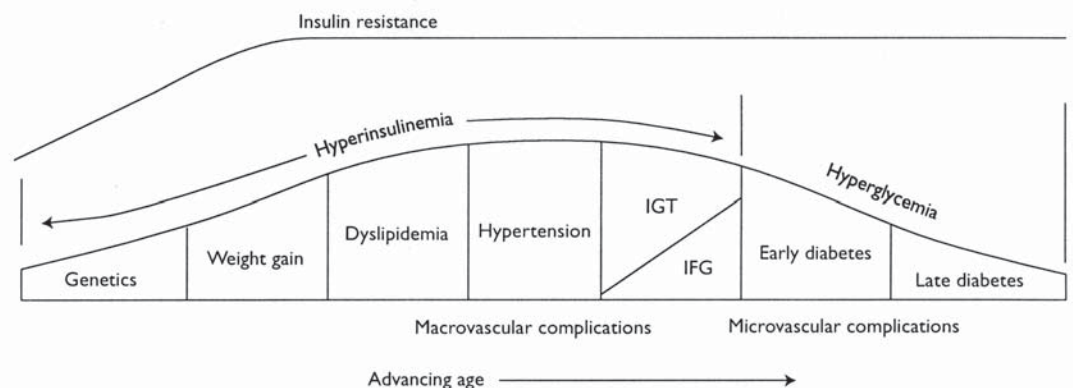
Type 2 Diabetes: Is an ounce of rosiglitazone worth a pound of cure?

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Is a consistently progressive disease such as type 2 diabetes preventable? Once diagnosed, can the progressive nature of this disease be delayed or controlled? At first glance, recent literature involving the use of rosiglitazone in diabetes may lead us to believe that these are, in fact, achievable aspirations and not just dreams. But what do the finer details of this literature actually show and how do we incorporate these findings into our daily practice?

Type 2 diabetes is the fifth leading cause of death in the United States, with associated healthcare costs estimated at more than \$130 billion/year.¹ The pathogenesis of type 2 diabetes is characterized by progressively increasing insulin resistance and hypersecretion of insulin from pancreatic beta cells, culminating in an inability of insulin production to overcome insulin resistance (see Figure 1).² Moreover, in line with the progressive nature of the disease, β -cell function declines consistently over time. Studies have shown that the deterioration in β -cell function can precede the development of type 2 diabetes by several years.³ The possibility of delaying or controlling this β -cell decline has prompted a number of studies in the area of diabetes prevention. One of these, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, examined the role of a thiazolidinedione (TZD), rosiglitazone, in diabetes prevention.⁴ This article aims to highlight some of the landmark studies in diabetes prevention, while concentrating on the results of the DREAM trial and its implications for the use of rosiglitazone in clinical practice.

Figure 1: Natural history of type 2 diabetes: disease progression²
(reprinted with permission)



TZDs are a class of antidiabetic agents that improve insulin sensitivity through activation of peroxisome proliferator-activated receptor-gamma ($PPAR\gamma$), concentrated in key targets for insulin action, such as adipose tissue, skeletal muscle, and the liver. The TZD class consists of two marketed drugs—rosiglitazone (Avandia[®]) and pioglitazone (Actos[®]). A third, troglitazone (Rezulin[®]), was the first member of this class to be FDA approved, but was removed from the market in 2000 due to liver toxicity.

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Table 1: Randomized control trials studying the effect of pharmacologic and non-pharmacologic interventions on the development of type 2 diabetes

Study	N	Design	Patient Population	Intervention	Duration of study	Relative risk reduction of developing diabetes
FINNISH Diabetes Prevention Study ¹³	522	Randomized controlled trial	<ul style="list-style-type: none"> age 40-65 BMI 25 FPG <140mg/dL + plasma glucose 140-200mg/dL 2h after a 75g PO glucose load 	lifestyle modification	3.2 years	58% (p<0.001)
STOP-NIDDM ¹⁰	1,429	Randomized, double-blind, placebo controlled trial	<ul style="list-style-type: none"> age 40-70 BMI 25-40kg/m² FPG 100-140mg/dL + plasma glucose 140-200mg/dL 2h after a 75g PO glucose load 	acarbose 100mg TID	3.3 years	25% (p=0.0015)
				metformin 850mg BID	2.8 years	31% (p<0.001)
				troglitazone 400mg Q D ¹¹ (withdrawn from market)	0.9 years	75% (p<0.001)
Indian Diabetes Prevention Program ²²	531	Randomized, controlled trial	<ul style="list-style-type: none"> age 35-55 FPG <126mg/dL + plasma glucose 140-199mg/dL 2h after a 75g PO glucose load 	lifestyle modification	3 years	28.5% (p=0.018)
				metformin 500mg Q D		26.4% (p=0.029)
				lifestyle modification + metformin 500mg Q D		28.2% (p=0.022)
TRIPOD ¹¹	266	randomized, double-blind, placebo controlled trial	<ul style="list-style-type: none"> age 18 Hispanic women with diagnosis of gestational diabetes within last 4 years sum of 5 oral glucose tolerance test (OGTT) plasma glucose 62mg/dL 	troglitazone 400mg Q D	2.5 years	55% (p<0.01)
DREAM ^{4,12}	5269	randomized, double-blind, placebo controlled, 2x2 factorial design	<ul style="list-style-type: none"> age 30 FPG 110-126mg/dL + plasma glucose <200mg/dL 2h after a 75g PO glucose load <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> FPG <126mg/dL + plasma glucose 140-200mg/dL 2h after a 75g PO glucose load 	rosiglitazone 8mg Q D	3 years	60% (p<0.0001)
				ramipril 15mg Q D		9% (p=0.15)

Periodic monitoring of liver function is warranted with the use of TZDs

Fasting plasma glucose and 2-hour post-load glucose levels are predictive for the development of diabetes.

While liver toxicity is not deemed to be a class effect, periodic monitoring of liver function is warranted with the use of TZDs.^{5,6} Rosiglitazone and pioglitazone are FDA approved for treatment of type 2 diabetes as monotherapy or in conjunction with a sulfonylurea, metformin, or insulin, when diet and exercise do not result in adequate glycemic control. TZDs are also touted for slowing the progressive decline of pancreatic β -cell function,⁷ sparking debate about the potential use of these agents to delay or prevent diabetes.

The need for effective preventative strategies for type 2 diabetes is evident in the serious microvascular and macrovascular implications of poor glycemic control. The target population for most diabetes prevention trials include patients with impaired fasting glucose or impaired glucose tolerance, who are at increased risk for developing diabetes (see Figure 1). One study examining the incidence of diabetes in a Dutch population found that the odds ratios for developing diabetes were 10.0 (CI 6.1-16.5) for impaired fasting glucose, 10.9 (CI 6.0-19.9) for impaired glucose tolerance, and 39.5 (CI 17.0-92.10) for both.⁸ Both fasting plasma glucose and 2-hour post-load glucose levels were found to be highly predictive of the

Definitions Per the American Diabetes Association:

- **Normal fasting plasma glucose (FPG) is defined as <100mg/dL.**
- **Impaired fasting glucose (IFG) is defined as FPG 100-125mg/dL.**
- **Normal glucose tolerance is defined as <140mg/dL 2h post 75g glucose load.**
- **Impaired oral glucose tolerance (IGT) is defined as 140-199mg/dL 2h post 75g glucose load.**

Patients with impaired glucose tolerance or impaired fasting glucose have significant risk for developing diabetes, and thus are target populations for prevention of diabetes.

In the DPP study, 50% of the 1,079 patients in the lifestyle intervention arm achieved the goal weight loss of 7% or more at the end of 24 weeks. By the end of the study, 38% of patients maintained a weight loss of 7%.

Common reasons for stopping rosiglitazone in the DREAM trial included edema (4.8%), weight gain (1.9%), and physician advice (1.9%).

development of diabetes ($p<0.0001$). Therefore, diabetes prevention trials are mainly conducted in patients with impaired fasting glucose or glucose tolerance.

Many clinical trials have demonstrated that both non-pharmacological and pharmacological treatments may be effective in this patient population to prevent progression to type 2 diabetes (see Table I). As can be seen in Table I, intensive lifestyle intervention with diet and exercise has proven to be a safe and effective means of preventing diabetes. However, it is important to note the extent of the effort that was involved on the part of healthcare providers in these lifestyle modifications. In the Diabetes Prevention Program (DPP) study, for example, patients were expected to achieve a 7% reduction in body weight through diet in conjunction with at least 150 minutes/week of moderate-intensity exercise.⁹ Patients underwent a 16-lesson curriculum detailing dietary, exercise, and behavior modifications. This curriculum was taught on a 1-to-1 basis for the first 24 weeks, followed by group sessions thereafter. Such intensive lifestyle modifications clearly require an extensive utilization of both labor and resources.

The DREAM trial was a double-blind, randomized clinical trial designed to prospectively assess whether rosiglitazone or ramipril prevents the progression of type 2 diabetes in patients at high risk.^{4,12} The reader is referred to reference 12 for the results of the ramipril arm. The trial was conducted in a 2x2 factorial design, with 5,269 patients randomized to either ramipril, rosiglitazone, or both, for a period of 3 years. The primary outcome measured in the study was newly diagnosed diabetes or death, and secondary outcomes included a composite of cardiac and renal events, glucose levels, and regression to normoglycemia.

Treatment with rosiglitazone 8mg daily demonstrated a relative risk reduction of 60% (HR 0.40, CI 0.35-0.46, $p<0.0001$) in the primary outcome of newly diagnosed diabetes or death.⁴ The absolute risk reduction between the treatment groups was 14.4%, which translates into a number needed to treat of 7. These results show a relative risk reduction similar to that attained by lifestyle modification using diet and exercise in the DPP study⁹ and the Finnish Diabetes Prevention study¹³ (both 58%) and that attained by troglitazone (75%) in the Diabetes Prevention Program.¹⁴ As would be expected, patients treated with rosiglitazone had a higher rate of regression to normoglycemia than placebo ($p<0.0001$).⁴

While the rosiglitazone results seem remarkably promising, other findings in the study are equally noteworthy.⁴ Patients treated with rosiglitazone demonstrated a 37% increase in the secondary outcome of a composite of cardiovascular events (2.9% rosiglitazone vs. 2.1% placebo, $p=0.08$). Furthermore, there was a statistically significant increase in the incidence of confirmed heart failure among patients treated with rosiglitazone (0.5% rosiglitazone vs. 0.1% placebo, HR=7.03, CI 1.60-30.9, $p=0.01$). In addition, patients treated with rosiglitazone averaged a 2.2kg increase in body weight compared to placebo ($p<0.0001$).

Thus, this trial raises many important questions. Does the use of rosiglitazone in patients with elevated fasting plasma glucose or impaired glucose tolerance actually prevent diabetes or only delay its onset? Since the duration of the DREAM trial was only 3 years, it is difficult to conclusively determine whether rosiglitazone prevented diabetes. There exists a possibility that progression to diabetes was actually masked by the plasma glucose-lowering effects of this medication. DREAM trial investigators attempted to answer this question with a post-trial "washout" period of 2-3 months. During this period, patients on rosiglitazone who did not develop diabetes were switched to placebo and

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TZDs cause significant weight gain. One study found that over 52 weeks, pioglitazone 45mg and rosiglitazone 8mg were associated with a 2.6kg and 2.9kg weight gain, respectively.²⁰ Clinically, weight gain is more dramatic when these drugs are used in combination with insulin.²⁰

TZDs as monotherapy for diabetes caused pedal edema at a rate of 3-5%.²⁰

TZDs are contraindicated in patients with NYHA heart failure class III and IV. Caution is warranted in patients with class I and II; start with lower doses and monitor carefully for edema.

Combination therapy with insulin and TZDs leads to an increased risk of heart failure.²⁰

Pioglitazone and rosiglitazone have similar effects on glycemic control but not on lipids. One head-to-head study found that pioglitazone increased HDL levels by 14.9% compared to 7.8% with rosiglitazone. Also, pioglitazone decreased triglycerides by 12% whereas rosiglitazone increased them by 14.9%. It is unknown how these differences in surrogate markers translate to cardiovascular risk reduction.

scheduled for a repeat oral glucose tolerance test at the end of the washout. When published, the results of this washout period may help us to understand if the actual pathogenesis of the underlying disease was improved or if progression to diabetes was simply masked.

Lastly, the issue of the effect of rosiglitazone on cardiovascular outcomes in the DREAM trial needs to be addressed. Although a secondary outcome, patients receiving rosiglitazone demonstrated a trend toward increased risk of cardiovascular outcomes and a 7-times higher risk of confirmed heart failure.⁴ In addition, there was also a considerable weight gain averaging 2.2kg (~5lbs) over the course of the study. It is noteworthy that the weight gain in patients treated with rosiglitazone did not plateau, but rather continued to increase throughout the 3-year period of study. This pattern of progressive weight gain is similar to that observed with the use of rosiglitazone in clinical practice. Considering that weight loss is one of the primary goals for cardiovascular risk reduction, this effect of rosiglitazone is contrary to the goal.

The ultimate effect of rosiglitazone on cardiovascular risk reduction is unknown. Studies demonstrating beneficial effects of TZDs have mostly been conducted on surrogate markers of cardiovascular morbidity, such as serum lipids, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic status.^{15,16} It is important to note that rosiglitazone and pioglitazone can have differing effects on surrogate markers such as LDL and triglyceride levels.¹⁷ Due to these differences, it is important to judge the cardiovascular risk or benefit of individual TZDs on the basis of clinical outcome studies.

To date, only 1 clinical trial has prospectively studied the effect of a TZD (pioglitazone) on cardiovascular risk reduction.¹⁸ The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study was a prospective, randomized, placebo-controlled, secondary prevention trial that evaluated the effect of pioglitazone on patients with evidence of macrovascular disease over a period of 2.8 years.¹⁸ In this study, pioglitazone showed a statistically significant difference in the combined secondary endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke ($p=0.027$), but failed to show a statistically significant reduction in the primary endpoint of a composite of cardiovascular morbidity and all-cause mortality. There are currently no published clinical trials that have assessed the effect of rosiglitazone on cardiovascular outcomes. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study is an ongoing trial that examines cardiovascular event reduction with rosiglitazone in combination with either metformin or a sulfonylurea, but not monotherapy.¹⁹ The study is expected to be completed in 2009.

Edema and weight gain are the most common side effects associated with TZDs. The edema accompanying TZD use has raised concerns regarding the development of heart failure, although the actual incidence of heart failure in clinical trials was low (~1%).²⁰ In clinical trials evaluating the safety and efficacy of the TZDs, patients with New York Heart Association (NYHA) class III or IV heart failure were excluded. The American Heart Association and American Diabetes Association consensus statement regarding the use of TZDs states that they should not be used in NYHA class III or IV heart-failure patients and should be used with caution in patients with NYHA class I and II heart failure²⁰. Their recommendations for patients with diabetes and 1 or more risk factors for heart failure or asymptomatic patients with an EF <40% are to start at lower doses and monitor patients closely for edema and weight gain.

The significant public-health and economic burden of type 2 diabetes has resulted in many clinical trials examining drugs aimed at its prevention. Evidence that β -cell dysfunction often precedes development of type 2 diabetes by a number of years

Current UW Medicine Patient Charge For Antidiabetic Drugs

- Acarbose 50mg TID: **\$76.50**
- Metformin 500mg BID: **\$8.15**
- Pioglitazone 30-45mg QD: **\$188.25-189.85**
- Rosiglitazone 4-8mg QD: **\$105.55-193.10**

Antidiabetic drugs that have proven beneficial in delaying or preventing progression to diabetes include metformin, acarbose, troglitazone (no longer available), and most recently, rosiglitazone.⁹⁻¹¹

There are currently differing clinical opinions about the use of TZDs for diabetes prevention.

In the absence of studies that shed light on rosiglitazone's ultimate effects on cardiovascular outcomes, the safety of using rosiglitazone long-term for the purpose of diabetes prevention is unknown.

The American Diabetes Association's recommendation is to hold off on using drugs for prevention of diabetes until cost-effectiveness data on reduction of diabetes-associated morbidity and mortality is available.

necessitates longer follow-up periods in diabetes prevention studies to differentiate disease-modifying vs. disease-masking effects of drug therapies. Results with rosiglitazone have shown the most promising results for diabetes prevention from drug therapy; however, the accompanying weight gain, edema, potential increased risk of heart failure, and considerable cost (see sidebar) of this agent raise questions about its use. Metformin and acarbose also show promise in diabetes prevention, but may be limited by gastrointestinal or other side effects associated with their use. The American Diabetes Association's recommendation is to hold off on using drugs for prevention of diabetes until cost-effectiveness data on reduction of diabetes-associated morbidity and mortality is available.²¹ The extent of diet and exercise interventions made in the DPP and FINNISH trials were intensive and required a great deal of resource utilization and patient commitment. Nevertheless, they were able to achieve an impressive reduction in progression to diabetes, in addition to modest weight loss and other benefits associated with increased physical activity. Until further information becomes available regarding the safety and cost-effectiveness of drug therapy for diabetes prevention and reduction of diabetes-associated morbidity and mortality, we should continue to encourage lifestyle interventions in our high-risk patients, while observing one of the principle teachings of medicine, *Primum non nocere*, "First, do no harm."

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(continued on back page)

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Candesartan (Atacand)	Tablet: 4mg, 8mg, 16mg, 32mg	Angiotensin II receptor antagonist	Hypertension; Heart failure.	Individualized.
Cinacalcet (Sensipar)	Tablet: 30mg, 60mg, 90mg	Calcimimetic	Secondary hyperparathyroidism; Hypercalcemia	30mg PO once or twice daily.
	Restricted to use by Nephrology Service for patients who are refractory/intolerant to vitamin D. Prescriber must obtain authorization from insurer for patient prior to initiating therapy.			
Ciprofloxacin/dexamethasone (Ciprodex)	Otic Solution: 0.3%/0.1% (5mL, 7.5mL)	Steroid/antibiotic combination	Acute otitis externa	3 drops in affected ear BID x 7 days.
Clindamycin (Clindesse)	Cream, vaginal: 2% (5g)	Antiinfective	Bacterial vaginosis	1 applicatorful intravaginally x 1.
Herpes zoster vaccine (Zostavax)	Injection: single-dose vials	Vaccine	Herpes zoster prevention	A single dose administered SubQ.
Levetiracetam (Keppra)	Injection: 100mg/mL (5mL)	Anticonvulsant	Adjunctive therapy for partial-onset seizures	500mg BID infused IV over 15 minutes.
	Prescribing restricted to Epilepsy Service physicians. Use for refractory status epilepticus and for patients established on oral levetiracetam therapy placed on NPO status is unrestricted.			
Formulary Deletions				
Clindamycin (Cleocin)	Clindamycin vaginal ovules were replaced by Clindesse [®] brand of clindamycin cream.			

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

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