What's New *in Clinical Research*

This new department features articles discussing recent developments in drug therapy, as well as review articles on specific drug therapies or disease states. Articles will discuss new drugs, new indications for existing drugs, and large, multicentre Phase III and IV trials.

All articles have been reviewed by our board of editorial consultants.

Current Research on the Prevention and Treatment of Type 2 Diabetes

1. University of British Columbia, Vancouver, British Columbia.
2. *Institut universitaire de cardiologie et de pneumologie de Québec, Hôpital Laval*, Ste-Foy, Quebec.

By Keith Dawson[1] MD, FRCPC and Claude Garceau[2] MD, FRCPC

The incidence of diabetes mellitus, which affects approximately 5% of adults worldwide,[1] has increased greatly during the past 20 years.[2] In particular, there has been an alarming rise in the incidence of type 2 diabetes, which is attributable to the rapid increase in obesity rates and the aging of the population.[3] In light of these demographic factors, it is imperative that healthcare professionals provide optimal treatment to their patients not only to manage diabetes and prevent its complications, but also to prevent its development in the first place.

A number of lifestyle and pharmacological interventions are known to be effective in helping patients optimally manage their glycemic levels. There are also emerging data to suggest that pharmacotherapy can be effective in preventing the progression of disease from pre-diabetic states (*e.g.*, impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) to overt type 2 diabetes.

This review will briefly review the impact of type 2 diabetes and provide a brief discussion of the disease's pathophysiology. The focus will then shift to treatment modalities, focusing on the results of recent landmark clinical trials in the prevention and management of type 2 diabetes.

THE IMPACT OF TYPE 2 DIABETES

The impact of type 2 diabetes—a chronic, progressively worsening disease—is well documented. There are associations with cardiovascular disease—the primary cause of death in type 2 diabetes—significant reductions in life expectancy,[4] and a high morbidity load. Hypertension, dyslipidemia, and macrovascular and microvascular events (*e.g.*, retinopathy, neuropathy) are all common complications that seriously compromise patients' quality of life and place enormous burdens on the healthcare system.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes is a metabolic disorder that is characterized by a progression of hyperglycemia caused by "defective insulin secretion, insulin action or both."[5] The disease's dynamic quality makes it especially challenging to identify initially and, subsequently, demands both careful monitoring and timely therapeutic responses to its progression.

While the precise pathophysiology of type 2 diabetes is not understood, it typically results from a prolonged period during which the individual undergoes IFG and/or IGT. Recent research has shown that glucose deterioration occurs in a stepwise fashion.[6] In a three-step process, glucose levels first begin to progressively increase in the daytime postprandial period, followed by the morning period, and lastly in the

overnight fasting period. These key stages in the progression from postprandial to fasting hyperglycemia, and finally to overt diabetes, can be seen as part of a continuum that begins long before the disease becomes clinically evident.

Insulin resistance (inability of insulin to adequately facilitate the uptake or use of glucose) is thought to be a major factor in the disease's development. Impairment of insulin secretion also plays a key role.

Initially, if a patient experiences insulin resistance, the pancreas compensates by producing more insulin. This may be initially sufficient to control glycemia. Over time, however, the pancreas becomes unable to produce enough insulin to continue to overcome the resistance, leading to the development—and subsequent progression—of type 2 diabetes. The vicious cycle then continues, as elevated glucose further impairs pancreatic beta-cell function, which, in turn, reduces insulin production.

Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) has shown that decline in β-cell function is directly correlated with the duration of disease and suggests that the decline actually typically begins long before the diagnosis of diabetes is made.[7]

These insights serve to emphasize the potential importance of long-term glucose control to help preserve β-cell function. Indeed, Harris *et al* observed that glycemic control, for type 2 diabetes patients, "eroded significantly with increasing duration of diabetes in spite of increasing therapeutic intervention."[8]

TYPE 2 DIABETES: THE CHALLENGES OF MANAGEMENT

Clearly, type 2 diabetes confronts clinicians with complex and enduring management challenges, including identifying patients at risk of developing the disease, despite the likelihood of their condition (*e.g.*, IFG and/or IGT) being asymptomatic. Once the disease develops, implementing and maintaining a successful and optimal treatment strategy involving both nonpharmacologic and pharmacologic interventions is also challenging. In fact, in spite of increasing therapeutic intervention, glycemic control has been found to progressively diminish with the increasing duration of the disease,[8] a result that is consistent with the UKPDS clinical findings about the progressive nature of type 2 diabetes.[7]

The goals of management in type 2 diabetes are therefore threefold: to improve A1C levels, to slow progression of diabetes, and to reduce complications. However, before arriving at these goals, one should consider ways by which the risk of type 2 diabetes can be reduced.

PREVENTION OF TYPE 2 DIABETES

The importance of lifestyle intervention, with an emphasis on diet and fitness goals, has become widely accepted as an important component in preventing the development of type 2 diabetes. In the Diabetes Prevention Program (DPP), researchers set goals of 7% weight loss and 150 minutes of physical activity per week for patients in the "lifestyle intervention" arm of the study. Following this protocol resulted in a 58% reduction in the incidence of type 2 diabetes.[9] However, the success of the lifestyle interventions in the DPP reflected, to a certain degree, the intensity with which participants were monitored and received professional assistance and guidance in adhering to program goals. The extent to which primary-care physicians, who are predominantly charged with the management of type 2 diabetes, can hope to achieve such effective adherence as was found in the DPP study—and achieve the concomitant benefits of lifestyle intervention—is seriously in doubt.

There exists, then, a pressing need for additional means of early and effective intervention to supplement lifestyle modification as a means of preventing the development of type 2 diabetes.

Three types of antihyperglycemic agents have also demonstrated an ability to prevent the development of type 2 diabetes.

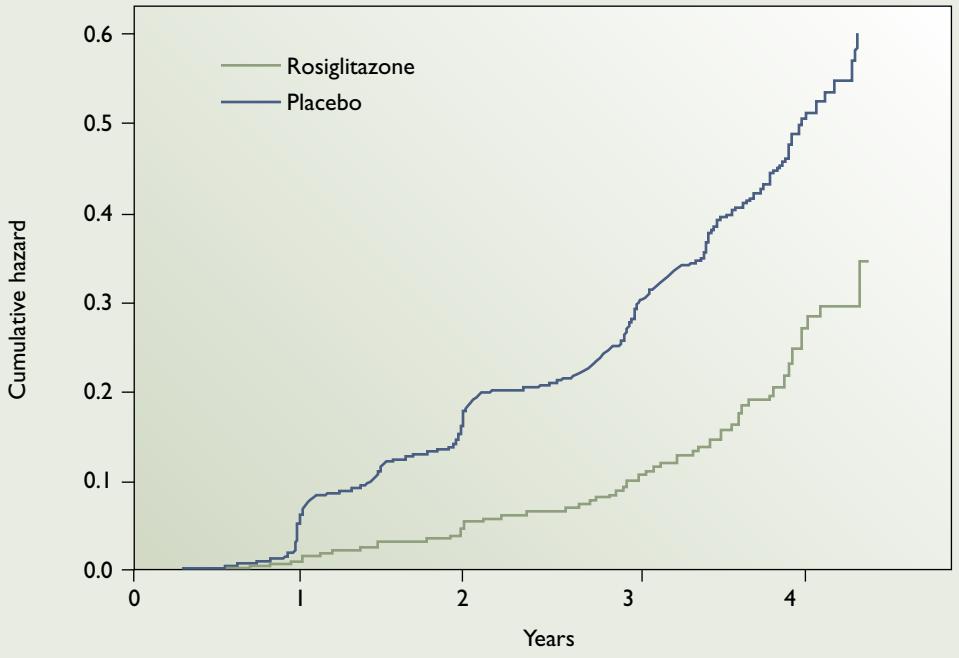
The alpha-glucosidase inhibitor acarbose was investigated in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),[10] which randomized 1,429 patients with impaired glucose tolerance to acarbose 100 mg t.i.d. or placebo.

For the primary endpoint of development of diabetes, acarbose reduced the relative risk by 25% versus placebo (p=0.0015). Furthermore, acarbose significantly increased reversion of impaired glucose tolerance to normal glucose tolerance ($p < 0.0001$).

Similarly, the DPP also included a metformin arm. Compared to placebo, metformin was found to reduce the risk of type 2 diabetes by 31% among 3,234 men and women with a body mass index of 34 ± 6.7 kg/m^2 and IFG or IGT.[11]

In the washout phase, which averaged 11 days, there was a partial loss of efficacy of metformin in preventing diabetes compared to placebo.[12] The rate of diabetes increased by 5.4% in the metformin group compared to a 3.3% increase in the placebo group, but

FIGURE 1 **DREAM Study: Time to Occurrence of Type 2 Diabetes or Death**[13]



Number at risk

Placebo	2,634	2,470	2,150	1,148	177
Rosiglitazone	2,635	2,538	2,414	1,310	217

metformin continued to prevent diabetes in 25% of patients in the metfornin group.

More recently, the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) study evaluated the efficacy of rosiglitazone 8 mg daily versus placebo in preventing type 2 diabetes among 5,269 adults, aged 30 or more, with IFG or IGT or both.[13] Over the trial's three-year duration, rosiglitazone at 8 mg daily reduced the risk of diabetes or death (primary endpoint) by 60% compared to placebo (Figure 1). The number needed to treat (NNT) was approximately seven; for every seven people with IFG or IGT who are prescribed rosiglitazone for three years, one will be prevented from developing diabetes.[13]

In addition to the primary endpoint result, rosiglitazone also increased the likelihood of regression to normoglycemia by about 70-80% compared to placebo. Figure 2 shows the distribution of patients in the two treatment arms with diabetes, IFG or IGT and normoglycemia (as defined as fasting plasma glucose [FPG] < 6.1 mmol/L).[13]

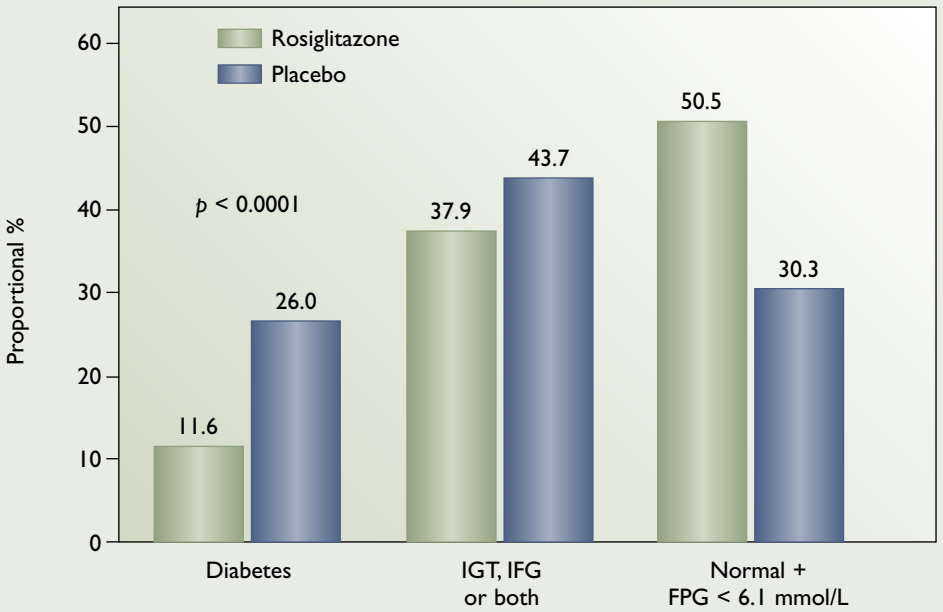
In a washout phase where medications were stopped for three to six months, there was a similar rate of diabetes in the rosiglitazone and placebo groups.[14] When the trial and washout data are analyzed together, there is an overall benefit to treatment with rosiglitazone for a median of three years.

PHARMACOLOGIC MANAGEMENT OF TYPE 2 DIABETES

As is the case with prevention, the cornerstone of management of type 2 diabetes is lifestyle modification. However, primary-care physicians have identified noncompliance with diet (72%) and exercise (71%) as the most common barriers to achieving glycemic targets through lifestyle modification.[8]

Further complicating treatment is the problem of "clinical inertia": whereby physicians, while recognizing problems, fail to act or to alter therapy appropriately.[15] According to Phillips *et al*, physicians are able to identify patients failing to meet their glycemic targets, but tend to overestimate the effectiveness of the care that they are providing.[15] This misinterpretation can lead physicians to rationalize their continued emphasis on compliance with lifestyle modifications, even though they recognize that patients' failure to comply is responsible for their inability to control their diabetes. Beyond continuation of that ineffective treatment course, many

FIGURE 2 Proportion of Participants who Developed Diabetes, Regressed to Normal, or Continued to Have IFG, IGT or Both (DREAM Study)[13]



physicians seem to be unaware of and, thus, at a loss to prescribe alternative treatments.[15]

The Canadian Diabetes Association (CDA)'s clinical practice guidelines recommend that the management of type 2 diabetes patients should aim to achieve glycemic levels as close to normal as possible, as early as possible.[5] Thus, if those with type 2 diabetes are not successful in achieving glycemic targets through lifestyle changes within two to three months, the CDA guidelines recommend the initiation of antihyperglycemic agents with concomitant lifestyle counselling.[5]

There are a number of pharmacotherapeutic agents available to Canadian physicians and their patients. The choice of antihyperglycemic agent(s) should be based on the individual patient and an understanding of the individual profiles of the various agents.

The agents recommended by the Canadian guidelines include metformin, sulfonylureas (*e.g.*, gliclazide, glyburide, glimepiride), alpha-glucosidase inhibitors (*e.g.*, acarbose), TZDs (*e.g.*, pioglitazone, rosiglitazone) and insulin.[5] The following section details recent findings with the TZD class of agents.

TZDs. The American Heart Association (AHA) and American Diabetes Association (ADA) 2003 consensus statement identified pioglitazone and rosiglitazone as effective agents in achieving glycemic goals and in reducing diabetes-related end-organ disease.[16] TZDs are indicated either as monotherapy or in combination with sulfonylurea or metformin when lifestyle interventions and single agents do not produce adequate glycemic control.

In addition to lowering blood glucose, the AHA/ADA assert that both drugs "may benefit cardiovascular parameters, such as lipid, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic status."[17,18]

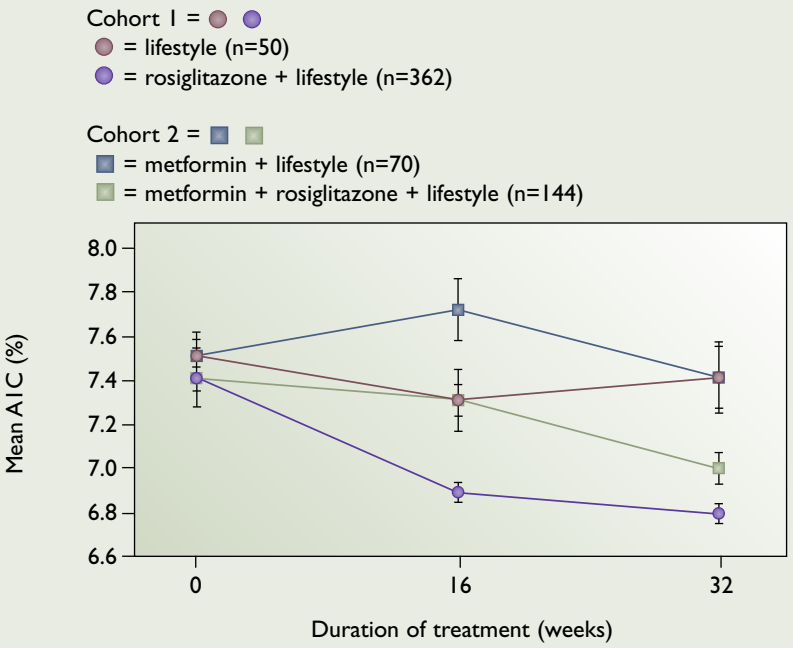
TZDs are not associated with hypoglycemia. However, they are contraindicated in those with either hepatic dysfunction or pronounced cardiac failure.

Leiter *et al* evaluated the efficacy of rosiglitazone in 705 patients with type 2 diabetes treated in primary care in Canada.[19] The study was comprised of two separate comparisons: lifestyle modifications alone (n=64) versus rosiglitazone plus lifestyle modifications (n=405) among drug-naïve patients; and metformin at augmented doses plus lifestyle modifications versus metformin plus addition of rosiglitazone plus lifestyle modifications among metformin-treated patients.

In the first comparison, mean change in A1C from baseline at 32 weeks (primary efficacy variable), treatment with rosiglitazone resulted in a decrease from a baseline A1C of 0.62% ($p < 0.001$), while there was no significant reduction in the lifestyle alone group (Figure 3).

In the second comparison, the combination of rosiglitazone with metformin resulted in a significant decrease

FIGURE 3 Changes in A1C Over Time[19]



in AlC compared with metformin. Adding rosiglitazone to metformin reduced A1C from 7.5 to 7.0%, while augmenting the dose of metformin alone resulted in a reduction from 7.5 to 7.4% (Figure 3). The results suggest then that combining rosiglitazone and metformin is a more effective approach than the usual strategy of maximizing the dose of metformin monotherapy.

Rosenstock *et al* also evaluated the efficacy of rosiglitazone/metformin combination therapy in a multicentre, open-label trial involving 190 patients with an A1C greater than 11% or FPG greater than 15 mmol/L.[20] Patients in this study initially received the rosiglitazone/metformin therapy in a 4 mg/1000 mg fixed-dose combination therapy. The dose was subsequently uptitrated in increments of 2 mg/500 mg at four-week intervals, to a daily dose of 8 mg/2000 mg or the maximum tolerated dose.

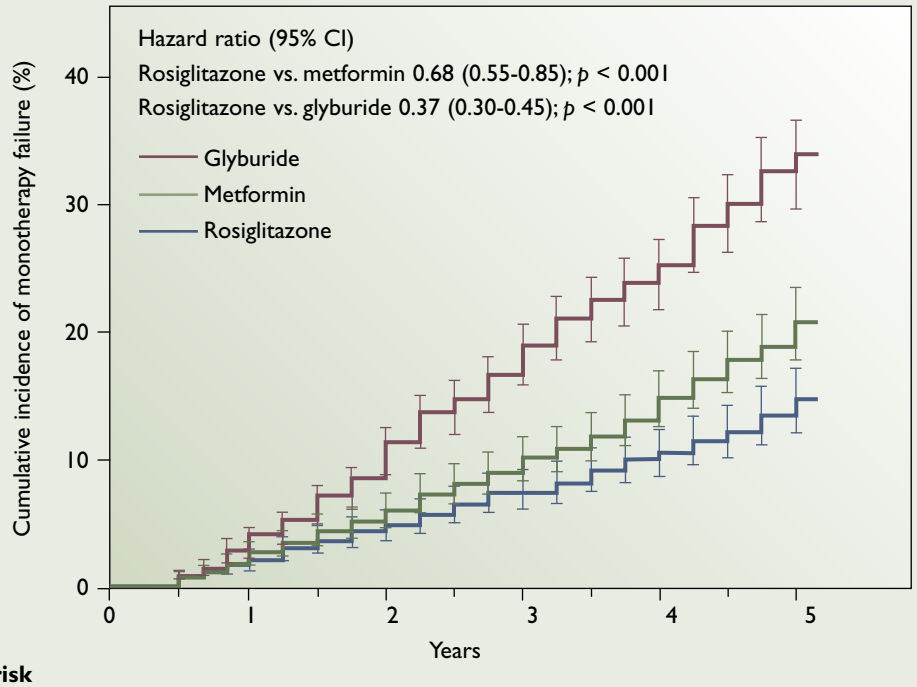
At 24 weeks, a clinically significant mean reduction in A1C from 11.8 to 7.8% ($p < .0001$) and a mean FPG reduction from 16.9 to 9.2 mmol/L ($p < .0001$) were observed. Nearly half of the patients reached an A1C level less than 7% and nearly one-third reached an A1C level of 6.5% or less. In addition, a clinically significant reduction in FPG (of 5.2 mmol/L) was observed after four weeks of fixed-dose combination therapy.

In a subsequent multicentre trial, Rosenstock *et al* studied the efficacy of rosiglitazone/metformin combination therapy versus monotherapy with either rosiglitazone or metformin in a double-blind design.[21] Study subjects had an A1C between 7.5 and 11%, and FPG less than or equal to 15 mmol/L. Patients were randomized to receive an initial daily dose of rosiglitazone/metformin (fixed-dose combination) 2 mg/500 mg, metformin 500 mg, or rosiglitazone 4 mg; doses could be uptitrated to 8 mg/2000 mg, 2000 mg, and 8 mg, respectively.

After 32 weeks, patients on the rosiglitazone/metformin combination therapy achieved a 2.3% reduction in A1C. This result was significantly greater than reductions with metformin (–1.8%) or rosiglitazone (–1.6%) monotherapy. Target A1Cs of less than or equal to 6.5% or less than 7% were reached by more patients in the rosiglitazone/metformin group (60% and 77%) than the metformin (39% and 57%) or rosiglitazone (35% and 58%) groups. Furthermore, there was a significantly greater mean decrease in FPG with the fixed-dose combination therapy (–4.1 mmol/L) compared with metformin (–2.8 mmol/L; $p < 0.0001$) or rosiglitazone (–2.6 mmol/L; $p < 0.0001$).

Because it is desirable to slow or halt the progression of disease as soon as possible, it is desirable to consider the relative efficacy of possible first-line monotherapies in achieving this goal. A large (n=4,360) clinical trial, A Diabetes Outcome Progression Trial (ADOPT), recently evaluated rosiglitazone, metformin, and glyburide as initial treatment in recently diagnosed, drug-naïve patients with type 2 diabetes.[22]

FIGURE 4 Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years (ADOPT)[22]



Number at risk

Rosiglitazone	1,393	1,207	1,078	957	844	324
Metformin	1,397	1,205	1,076	950	818	311
Glyburide	1,337	1,114	958	781	617	218

The primary outcome of this study was time to monotherapy failure, defined as plasma glucose levels of more than 180 mg per deciliter (> 10.0 mmol/L) after an overnight fast. The mean duration of the study was 4.0 years.

The primary results showed that there was a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (Figure 4). This represents a risk reduction of 32% for rosiglitazone compared with metformin and 63% compared with glyburide.[22]

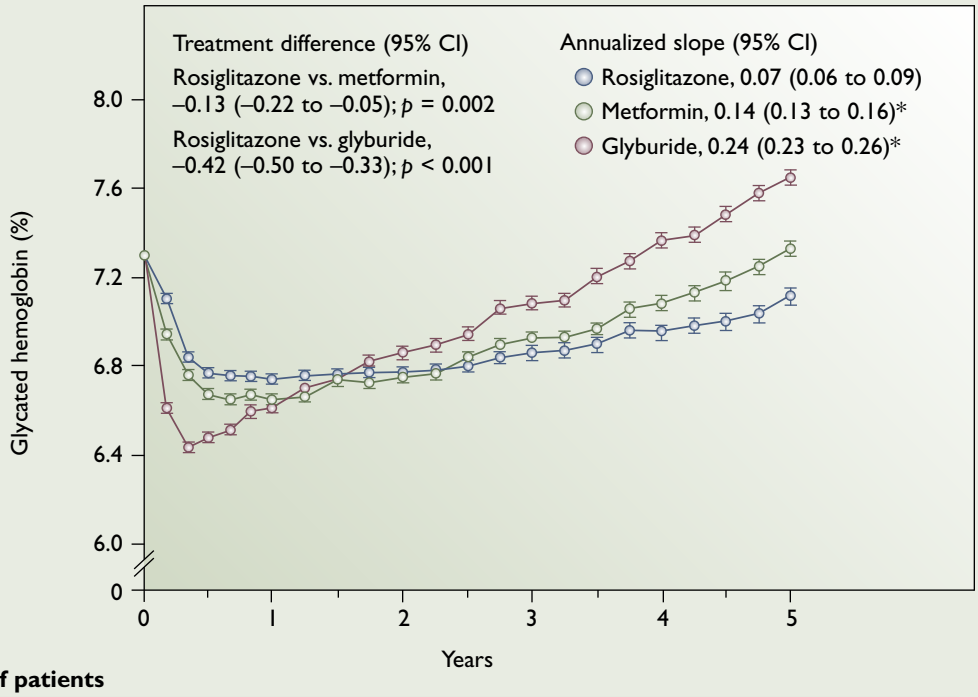
This result indicates that rosiglitazone is superior to metformin and glyburide in delaying the progressive loss of glycemic control. Indeed, rosiglitazone maintained a mean level of A1C at less than 7% longer (57 months) than metformin (45 months) and glyburide (33 months) (Figure 5). In addition, rosiglitazone was more effective in improving insulin sensitivity than either metformin or glyburide (Figure 6). There was also an indication that rosiglitazone was more effective in slowing the annual rate of decline in β-cell function compared to metformin. Further analysis is required to extract the significance of this result.

Although rosiglitazone was associated with weight gain, redistribution of body fat and varying patterns of adipokine release may account for the observed improvement in insulin sensitivity despite the weight gain. Subgroup analysis revealed that the rosiglitazone treatment effect was greater with older patients than metformin and amongst those with a larger waist circumference (> 110 cm). Rosiglitazone was more effective than glyburide in all subgroups.

As with any agent, when considering the use of an antihyperglycemic agent, one must weigh the potential risks against the expected benefit. In the case of rosiglitazone, some concern has been raised about associated weight gain and the possibility of increased risk of congestive heart failure (CHF). As well, the ADOPT study showed a 4.2% increase in extremity fractures in women taking rosiglitazone compared with metformin.[22] These findings remain to be clarified, but this was not an identified primary outcome in the study.

In the first Rosenstock study, the investigators wrote that the fixed-dose combination was well tolerated as a first-line therapy and no new tolerability issues were iden-

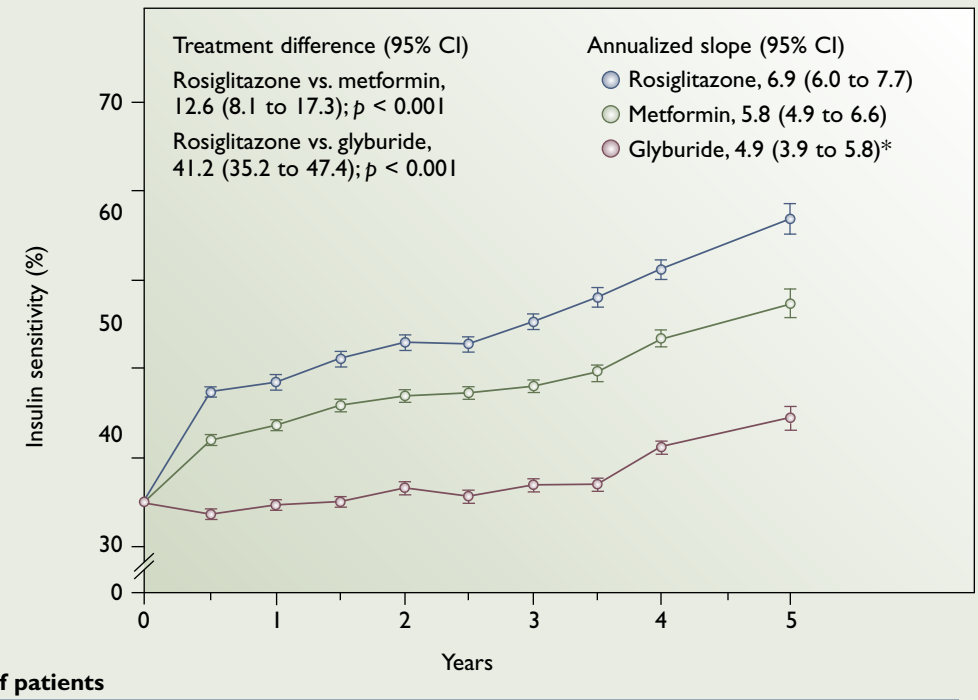
FIGURE 5 Changes in A1C Over Five Years by Treatment Group (ADOPT)[22]



Number of patients

Rosiglitazone	4,012	3,308	2,991	2,583	2,197	822

FIGURE 6 Changes in Insulin Sensitivity Over Five Years by Treatment Group (ADOPT)[22]



Number of patients

	3,634	3,193	2,776	2,367	2,025	820

tified. A mean increase of 2.6 kg in body weight was less than previously reported with rosiglitazone monotherapy and "considerably less than what might have been expected given the large improvement in glycaemic control."[20] In the DREAM study, the investigators stated, "for every 1,000 people treated with rosiglitazone for three years, about 144 cases of diabetes will be prevented, with an excess of four to five cases of CHF."[13]

In the ADOPT study, the authors found that the rate of CHF associated with rosiglitazone was similar to that in studies involving low-risk populations and to that associated with metformin, but higher than that associated with glyburide.[22]

CONCLUSION

More than 8% of adults worldwide have either IGT or IFG, and every year 5-10% of that group will develop diabetes with the concomitant disease burden. As the increasing prevalence of diabetes in an aging Canadian population places an increasing burden on a healthcare system that is already stressed, there is an urgent need for more effective intervention in the prevention and treatment of the disease. Recognition of the importance of early and effective glycemic control has led the CDA to recommend pharmacologic intervention when lifestyle modification has not achieved glycemic targets within two to three months. The evidence is accumulating showing the effectiveness and safety of rosiglitazone throughout the spectrum of disease. The DREAM study has shown that rosiglitazone can help prevent the emergence of type 2 diabetes in those with IFG and/or IGT; the ADOPT study showed that rosiglitazone is superior to metformin or glyburide monotherapy in delaying the progression of type 2 diabetes. Even so, these results do show that all tested monotherapies fail relatively quickly. The use of effective combination therapies is therefore imperative. Previous studies have shown that rosiglitazone is also effective as part of a combination antihyperglycemic regimen.

In optimizing the management of type 2 diabetes, evidence therefore indicates that rosiglitazone can play a major role at several stages of the disease.

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