

Insulin Therapy in Type 2 Diabetes: New Strategies and New Approaches

By Julio Rosenstock, MD



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We have entered an era of recognition that better metabolic control of diabetes results in significantly reduced risks for both microvascular and macrovascular complications.

Less recognized but also very important, is a growing body of evidence that early insulin replacement may induce beta cell “rest” and preserve beta cell function and, equally important, also may reduce cardiovascular risk. These fundamental benefits of insulin eventually may transform the insulin therapy paradigm in type 2 diabetes, assuming they are confirmed in further studies.¹ Nevertheless, as physicians and patients struggle to achieve increasingly stringent glycemic targets, it is time to recognize that the earlier implementation of insulin therapy is an idea whose time has come.

Patterns and timing of insulin use in type 2 diabetes have changed minimally or not

at all in the past 20 years, as demonstrated by National Health and Nutrition Examination (NHANES) data from 1988-1994 and 1999-2000 (Figure 1).² These patterns persist despite the development of insulin analogues that more closely mimic natural physiologic response than older insulins and despite substantial clinical experience with structured insulin dosing algorithms using basal, basal-bolus, and premixed insulins.

The plateau in insulin use likely reflects clinical inertia coupled with physicians’ dependence on the traditional type 2 diabetes stepwise treatment paradigm in which lifestyle therapy is followed by a single oral agent selected from one of many approved classes of antidiabetic agents. With progression of the disease, a second oral agent typically is added, sometimes followed by a third agent, or the practitioner may decide to add insulin. As a result, patients starting insulin tend to have relatively advanced diabetes.

A recent study evaluated the addition of low-dose insulin glargine versus maximum-dose rosiglitazone in patients on combined sulfonylurea and metformin therapy. These patients had type 2 diabetes for an average of 8 to 9 years and mean baseline A1C levels of ~8.8%. Both treatments resulted in similar A1C improvements of -1.7% and -1.5%, respectively. However, when baseline A1C levels were $\geq 9.5\%$, significantly greater reductions were seen with insulin glargine than with rosiglitazone.³

The demographics of this study are typical of most clinical trials evaluating insulin preparations. For instance, entry criteria call for baseline A1C levels between 7.5% and 10.5%; mean A1C levels are typically between 8.5% and 9.0%, and as a result, participants tend to have had diabetes for nearly a decade before insulin use

About this Program

Optimizing Insulin Use in Type 2 Diabetes

It is well known that macrovascular and microvascular complications are common among patients with type 2 diabetes, and research has shown that early diagnosis, initiation of therapy, and good glucose control are linked directly to prevention or reduction in progression of these complications.

Equally well known are the myriad of reasons why healthcare providers and their patients with type 2 diabetes are hesitant to initiate insulin therapy, including concerns about hypoglycemia and weight gain, and the fear and stigma associated with injectable insulin.

Insulin IDEAS (Innovations in Diabetes: Emerging Approaches and Strategies™) is a continuing medical education (CME) initiative designed for endocrinologists, internists and family physicians with heavy caseloads of patients with type 2 diabetes, and diabetes educators. The program features a series of newsletters and telewebconferences that provide clinicians with a variety of opportunities to explore the latest data on optimizing insulin use in patients with type 2 diabetes and to translate that evidence into effective clinical practice.

In addition to this issue, the CME-approved newsletter—*Clinical Update: Type 2 Diabetes Management*—will be published in September and October.

The live, CME-approved telewebconferences will take place from June through October 2006. The series is divided into 2, case-based courses of 30 meetings each. *Course 1: Rationale for Use of Insulin Early in the Course of Type 2 Diabetes* illustrates the case of a woman who recently was diagnosed with diabetes and whose

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Statement of Need: More than 18 million people in the US are affected by diabetes, with the majority (>90%) having type 2 diabetes mellitus (T2DM). It is well known that macrovascular and microvascular complications are common among people with the condition, and research has shown that early diagnosis, initiation of therapy, and good glycemic control are linked directly to prevention or reduction in progression of these complications.

However, T2DM is associated with a long asymptomatic phase, and patients generally are not diagnosed until clinical macro- and/or microvascular complications are apparent. Furthermore, many T2DM patients are reluctant to initiate treatment because they are asymptomatic. Patients particularly are hesitant to start insulin therapy because of the stigma and fear associated with injectable insulin.

With the impending availability of numerous oral, injectable, and inhaled agents for the treatment of diabetes, physicians will need to know where and when each of these agents should be considered in the course of treatment. The availability of so many new options suggests that the multimodal approach to treatment will gain prominence and complexity in the years ahead, with clinicians prescribing various combinations of agents targeting different mechanisms of action in an attempt to provide a comprehensive response to the metabolic derangements of diabetes.

This trend makes it important that clinicians understand the mechanisms of action, efficacy and safety, beneficial and adverse effects, and practical considerations associated with both current and emerging treatment options so that they can make informed decisions about the optimal use of insulin in the management of patients with T2DM.

Intended Audience: This activity has been developed for endocrinologists, internists and family physicians with heavy caseloads of patients with type 2 diabetes, and diabetes educators.

Educational Objectives: At the conclusion of this educational activity, the participant should be able to:

- Apply what is known about the safety, efficacy, and utility of available and emerging options for insulin therapy to treatment decisions in individual patients
- Tailor pharmacologic therapy with oral agents and insulin to meet the glycemic control needs of individual patients with type 2 diabetes
- Outline the importance of good glycemic control in patients with type 2 diabetes and translate the evidence regarding the independent effects of insulin and antihyperglycemic drug therapy on cardiovascular disease risk into optimal patient management
- Discuss the key findings and clinical implications of the PROactive study

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is even considered.

What does this mean? First, glycemic control has been allowed to deteriorate by too much in these patients. They have accrued several years of hyperglycemic burden and presumably significant beta cell loss. Second, when physicians consistently see reports in clinical trials that insulin therapy is started only when A1C levels reach this point, they internalize the message that this is reasonable—and perhaps unavoidable—practice. Last, waiting this long to start insulin therapy leads to higher insulin requirements, regardless of the regimen used, and the need for more complex regimens.

Clinical inertia and delays in therapeutic transition

The reasons why insulin use is delayed are well documented. Physicians are concerned about the additional resources needed to train and manage patients. Patients are concerned about self-injection pain, lifestyle restrictions, and the perception that insulin use means their health has worsened beyond repair. Both physicians and patients are concerned about the risks of hypoglycemia and weight gain.⁴

The recently published Diabetes Attitudes, Wishes, and Needs (DAWN) study, a multinational survey of both healthcare providers and patients, found that US physicians and nurses prefer to delay insulin use for as long as possible. At the same time, they found that patients generally do not consider insulin an effective therapy, the one exception being among patients whose diabetes was relatively advanced.⁵ Clearly, knowing what contributes to insulin underuse does not easily translate into changed attitudes or treatment plans.

The concept of clinical inertia—the time that elapses between the recognition of a patient's problem and the point at which treatment is initiated—has taken hold in type 2 diabetes time-to-treatment transition analyses.⁶ In 2004, Brown and colleagues evaluated a large Kaiser Permanente Northwest population with type 2 diabetes (N=7208 courses of treatment over 8 years). They found that even these “well-controlled” patients accumulated literally years of hyper-

glycemic burden. This was assessed by averaging the time elapsed between treatment failure and restoration of normoglycemia in the context of the type 2 diabetes step-wise treatment model. For example, patients experienced a mean lapse of 8.6 A1C-months between lifestyle therapy failure and the transition to a single oral agent.

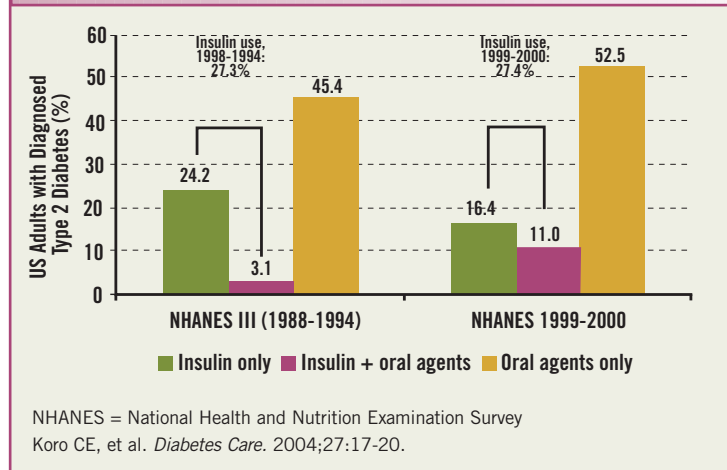
Individuals failing combination drug therapy spent 29.9 A1C-months with uncontrolled A1C. Overall, patients spent a mean of 5 years with A1C levels >8%, and 10 years with A1C levels >7%.⁷ This clinical hesitancy in moving to more aggressive treatment has been confirmed in other studies.^{6,8}

This year, the American Diabetes Association (ADA) has modified its A1C target. The goal, which is derived from interventional studies, remains <7%. Based on epidemiologic evidence, however, the new recommendation for individual patients is <6% (as long as this does not cause unwanted side effects such as hypoglycemia).⁹ A1C-lowering is now a “moving target” in type 2 diabetes management; the goal ultimately established will depend on the results of several, ongoing, large-scale trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Outcome Reduction with Initial Glargine Intervention (ORIGIN) studies.¹⁰ Each of these trials is evaluating the effect on CV outcomes of therapy directed toward achieving lower glycemic targets. It is certain that new strategies will be needed to maintain A1C levels <7%.

Initiating insulin: Options and strategies

The timing of insulin initiation should be a function of glucose goal targeting and beta cell preservation, not a function of type 2 diabetes duration. Ideally, progression through oral agents should take no longer than 2 or 3 years, so that beta cell reserves are present at insulin initiation.

FIGURE 1. NHANES: Treatment of Diagnosed Type 2 Diabetes in the US—Patterns of Insulin and Oral Agent Use



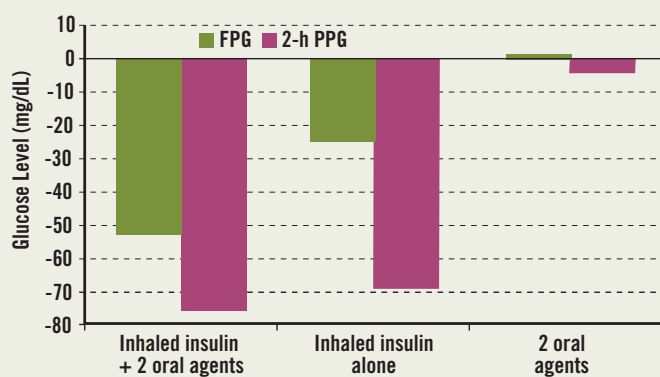
To illustrate, consider a typical case—a patient who started oral agents 6 years ago and is failing metformin and sulfonylurea therapy at maximally effective doses. This patient's A1C level has climbed gradually from 7.3% to 8.7%. It is likely that this patient would achieve an A1C of 7.3% or 7.4% on triple therapy—a level that is not at target but also not generally perceived as high enough to justify adding insulin. This is an example of clinical inertia, during which the treating physician waits for the patient's A1C to rise before taking the next step.

Supplemental basal insulin following dual therapy failure might have resulted in this patient achieving his/her A1C target. The well-established, treat-to-target strategies with insulin glargine—or, more recently, insulin detemir—offer clear strategies to reach A1C targets in the 7% range, with a lower risk for hypoglycemia than with NPH.^{11,12} Premixed insulins are another option, but may be less flexible and come with an increased risk for hypoglycemia.^{13,14}

Initiating insulin therapy to target postprandial hyperglycemia also is a validated approach that has been shown to be safe and effective—possibly more effective than basal insulin at decreasing A1C. A pilot study comparing the efficacy of metformin, basal insulin, or prandial insulin added to maximal sulfonylurea therapy in poorly controlled patients found that patients treated with prandial insulin experienced greater A1C reductions compared with those receiving metformin or basal insulin

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FIGURE 2. Mean Change in FPG and 2-hour PPG: Inhaled Insulin Added to 2 Oral Agents



Rosenstock J, et al. *Ann Intern Med.* 2005;143:459-558.

($P=0.025$).¹⁵ The use of prandial insulin, however, has not been widely implemented. Arguably, this can be attributed to the need for multiple daily injections, which could pose a substantial burden for patients new to insulin treatment.

Now there is another prandial insulin option to consider—inhaled insulin—which holds out the possibility of enabling earlier, more flexible, and more patient-acceptable insulin introduction than that associated with currently available insulins. Several studies have shown that patients receiving inhaled insulin prefer this therapy and experience greater short- and long-term satisfaction compared with patients taking subcutaneous insulin.^{16,17}

A recent trial involving 309 patients with type 2 diabetes on oral agent therapy with baseline A1C levels of 8% to 11% compared dry powder inhaled insulin added to existing oral agents versus inhaled insulin alone or continued oral agent therapy alone. Inhaled insulin significantly improved A1C levels (-1.7% when added to oral therapy, -1.2% when used alone; $P<0.001$). The results were particularly striking in that inhaled insulin showed a robust effect on both postprandial and fasting plasma glucose (PPG and FPG, respectively) (Figure 2), with a mean 76 mg/dL decrease in PPG and a mean 53 mg/dL decrease in FPG at 12 weeks.¹⁸ These findings are consistent with results obtained in other studies, as well as with results obtained from a pilot study evaluating injectable prandial insulin as initial insulin therapy following sulfonylurea failure.^{15,19,20}

This study design challenges prevailing treatment orthodoxy. Instead of first targeting FPG and initiating insulin with a basal or premixed regimen, the researchers targeted PPG with a rapid-acting dry powder inhaled formulation and found a serendipitous effect on FPG. The biologic explanation for this fasting effect is not known.

As we progress towards more stringent A1C targets, increased focus will be placed on achieving A1C goals in patients who are only reasonably well controlled—those with moderately elevated A1C levels $>7\%$. The findings of this study indicate that it is reasonable to consider moving beyond the standard practice of targeting FPG as the first step in insulin therapy. For some patients, it may be reasonable to start insulin treatment with prandial insulin, and inhaled insulin may have particular advantages as a prandial insulin.^{15,16,19,20} For these patients, it is possible that one dose of inhaled insulin prior to the main meal of the day may reduce A1C by 0.4% to 0.5%. In patients with higher initial A1C levels, 2- or 3-meal coverage may be advisable. This mirrors the approach currently taken by many practitioners of initiating insulin with bolus therapy administered before the individual meals associated with the highest PPG levels.²¹

Long-term studies to confirm the efficacy of inhaled insulin, as well as to examine its safety in certain patient populations (eg, those with asthma and other pulmonary conditions), are needed. It also remains the case that, regardless of which insulin is used first, chances are good that most patients with type 2 diabetes eventually will require a combination of basal and postprandial insulin.

Conclusion

Time spent by patients at and above the A1C threshold of 7% must always be thought of as time spent accruing hyperglycemic risk. The past 5 years have seen the

development of insulin analogues that more closely mimic healthy physiologic response, and results from multiple trials have provided physicians with safe, structured insulin dosing algorithms using both basal and prandial approaches. Based on the data and what is known about the natural history of type 2 diabetes, it is reasonable to suspect that insulin added earlier in disease progression will help decrease the amount of time spent in poor glucose control. Early insulin also may slow diabetes progression and provide CV benefit.

Although initiating insulin therapy with once-daily basal insulin is the best approach for many patients, some may benefit from insulin initiation with prandial insulin. Research has shown that prandial insulin, both injectable and inhaled, leads to decreases in both fasting and postprandial glucose increments. This approach may be useful particularly for patients with only moderately elevated A1C levels, for whom the addition of a new drug is not necessarily appropriate, but who still need to lower their glucose levels to target range. ■

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The Dual Role of Diabetes Therapy: Glycemic Control and Cardioprotection

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Center in Burlington, MA.

The prevention and treatment of cardiovascular disease (CVD) in individuals with type 2 diabetes is a medical challenge. While advances in CVD prevention and management have led to substantially lower mortality rates in the population as a whole, this decline has not crossed over to the diabetic population.¹ Insulin and anti-hyperglycemic drug therapy are now used to manage both acute hyperglycemia and to provide adjunctive CVD prevention. From a clinical standpoint, we have moved into a territory where we must consider the goals of diabetes management from 2 perspectives: that of an endocrinologist and of a cardiologist.

What aspects of the diabetic disease process are responsible for this unremitting CVD risk? Hyperglycemia is an obvious culprit, although nonglycemic factors such as endothelial dysfunction, inflammation, thrombosis, and sympathovagal imbalance also appear to play an important role.² It is well documented that elevated blood glucose levels confer cardiovascular risk. The United Kingdom Prospective Diabetes Study (UKPDS) found a 16% overall CVD decrease in participants assigned to intensive therapy. While this finding was of borderline statistical significance ($P=0.052$),³ the result was robust enough, in my view, to consider it clinically significant. An epidemiologic follow-up study found that myocardial infarction (MI) risk was significantly associated with glucose levels, with a 14% risk reduction for every 1% decline in A1C level.⁴

Thus, the case is strong for treating hyperglycemia as a means of reducing CVD risk. However, the tools in the arma-

mentarium are numerous, and the optimal approach to achieving euglycemia is not always clear. For this reason, it is critical for physicians treating patients with diabetes to gain a better understanding of available strategies, to understand current evidence regarding the independent effects of each therapeutic drug class on CVD risk, and to ascertain whether this impact is positive, negative, or neutral.

Insulin

Insulin has been well studied with respect to its impact on CVD risk reduction in diabetes. In addition to its effects on blood glucose lowering, insulin improves endothelial function in patients with poorly controlled type 2 diabetes.⁵ Insulin used to achieve normoglycemia also protects patients admitted to intensive care units (ICU) from excess mortality.

In a seminal study, intensive glycemic control achieved with insulin in the surgical

*The case is strong
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ICU resulted in a 32% reduction in mortality ($P<0.04$), even in patients without a prior diabetes diagnosis. In this case, the protective effect of insulin was particularly notable among patients requiring ≥ 5 days of hospitalization.⁶

A recent follow-up from the same researchers found that intensive insulin administered in the medical ICU significantly decreased morbidity, but not mortality. One exception to this finding was

among patients requiring a hospital stay of ≥ 3 days. Among these patients, intensive insulin significantly reduced both morbidity and mortality.⁷ The study's authors have suggested that one mechanism for insulin's clinical benefits in this setting might involve an alteration of the "inflammatory milieu" in CVD patients.

Along these lines, another recent study found that insulin significantly attenuated the increased levels of C-reactive protein and serum amyloid A, which typically follow acute MI.⁸

Unfortunately, the use of insulin as a cardiologic tool has been hampered by a longstanding debate in which one contingent has argued that insulin is atherogenic. This argument is fueled by epidemiologic studies demonstrating that elevated endogenous insulin levels are associated with CVD risk in patients with diabetes or prediabetes, and from observational studies suggesting that CVD risk is related to insulin therapy.⁹ The counterargument suggests that insulin resistance is the actual cause of increased CVD risk, with elevated endogenous insulin exerting a secondary effect.¹⁰

Two landmark clinical studies—the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)—support the case for insulin's beneficial effect. DIGAMI evaluated the effects of insulin-mediated glycemic control in patients with diabetes admitted to the hospital with acute MI. Patients with type 1 and type 2 diabetes were allocated to either standard treatment or to standard treatment combined with insulin therapy both during and posthospitalization. Investigators found a 28% relative reduction in mortality for patients randomized to insulin therapy.¹¹

A posthoc epidemiologic analysis of the DIGAMI follow-up study, DIGAMI 2, confirmed that elevated glucose levels in the postacute MI period were independently

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associated with high mortality rates. Unfortunately, DIGAMI 2 did little to confirm or deny the specific mortality benefits of post-MI insulin treatment in patients with diabetes. Postintervention blood glucose levels were similar across all 3 trial arms, making it all but impossible to evaluate the relative benefit of the different strategies applied.¹²

Furthermore, the remarkable benefit shown by the first DIGAMI study must be considered in the framework of standard post-MI therapy available at the time this study was performed (1990-1993).¹¹ DIGAMI 2 actually served to confirm the benefit of post-MI glucose control in a contemporary context, where current treatment strategies, such as aggressive LDL cholesterol lowering, multidrug antihypertensive therapy, and revascularization procedures, were administered to patients as needed.¹²

Most recently, the DCCT/EDIC 20-year results revealed significantly improved CVD outcomes associated with a prior 6.5-year period of intensive blood glucose lowering with insulin in patients with type 1 diabetes. This included a 42% decrease for any CVD event ($P=0.02$) and a 57% decrease in risk for nonfatal MI, stroke, or death from CVD ($P=0.02$).¹³ This risk reduction is particularly notable because EDIC participants all have type 1 diabetes, and consequently, have a lower prevalence of metabolic features such as obesity, dyslipidemia, hypertension, and insulin resistance than would be seen in a typical type 2 diabetes population. Thus, this study provided a unique opportunity to investigate the effect of insulin-induced euglycemia on CVD outcomes independent of potential effects from nonglycemic factors.

Sulfonylureas

There is a debate as to whether sulfonylureas (SUs) actually may have a negative effect on CVD outcomes. In the UKPDS, SUs conferred a nonsignificant risk reduction for CVD.³ Most recently, this question was addressed in a large retrospective cohort study, in which the investigators examined the relationship between CVD event rate and SU monotherapy use (versus

other diabetes drugs used as monotherapy) in patients with type 2 diabetes registered with the Saskatchewan Health administrative databases. Investigators found that first-generation SU users were at greatest risk for death, followed by glyburide users and metformin users (67.6 vs 61.4 vs 39.6 deaths/1000 person-years, respectively). The SU-associated risk increased in a dose-dependent manner.¹⁴

Based on this and on prior studies evaluating the relationship between SUs and CVD, it appears likely that SU therapy

There has been increasing interest in the role of postprandial hyperglycemia in CVD development.

is not the optimum antihyperglycemic drug of choice in patients with cardiovascular risk. However, it must be emphasized that whether these drugs actually have detrimental effects has not yet been determined.

Metformin

Unlike SUs, available evidence indicates that metformin, in addition to its blood glucose-lowering effects, is likely associated with reduced CVD risk. Metformin may be particularly effective in overweight patients with type 2 diabetes, as illustrated by the UKPDS metformin subgroup. In these patients, MI risk with intensive metformin therapy was reduced by 39% ($P=0.01$) compared with participants receiving conventional therapy.¹⁵ In the Saskatchewan Health Study discussed previously, investigators reported reduced risk for all-cause mortality (adjusted OR, 0.60; 95% CI, 0.49-0.74) and cardiovascular mortality (adjusted OR, 0.64; 95% CI, 0.49-0.84) in participants treated with metformin versus those treated with SUs.¹⁶

The mechanism of action of metformin on classic cardiovascular risk factors is

unknown, although it has been posited that its protective effect may be due to the moderate weight loss associated with the drug, to decreased insulin resistance, or to metformin's contribution to improved lipid profiles.¹⁷

Thiazolidinediones

Evidence is accruing that thiazolidinediones (TZDs) confer CVD benefit in the context of diabetes therapy. The PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) study recently reported promising results on the use of pioglitazone in patients with prior CVD. Participants treated with pioglitazone experienced decreased CVD events compared with individuals receiving other types of glucose-lowering therapy.¹⁸ Whether this was because the TZD-treated patients had a small but significantly greater mean A1C reduction, or whether pioglitazone improved CVD outcomes via nonglycemic mechanisms, remains to be determined.

Of note, despite PROactive's exclusion of individuals at risk for congestive heart failure (CHF), participants receiving pioglitazone had an increased rate of edema and heart failure.¹⁸ As Vivian A. Fonseca, MD, notes in his article on page 7, this may be due in part to the 45-mg maximum daily dose of pioglitazone administered by PROactive. This exceeds the pioglitazone dose currently considered safe for use in combination therapy, with evidence indicating that CHF risk is increased when high-dose pioglitazone and insulin are combined. CHF and weight gain are associated with TZD use and remain notable concerns for this drug class. Nevertheless, the PROactive study suggests that TZDs may be a good first-line treatment for secondary or tertiary prevention in patients with type 2 diabetes and prior CVD events.

Alpha-glucosidase Inhibitors

There has been increasing interest in the role of postprandial hyperglycemia in CVD development, particularly in light of evidence that individuals with impaired glucose tolerance (IGT) but without frank diabetes have an increased risk of CVD.¹⁹ In the STOP-NIDDM trial, acarbose was found to confer a 49% relative risk reduction for cardiovascular events in patients

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The PROactive Study

By Vivian A. Fonseca, MD



Dr. Fonseca is Professor of Medicine, the Tullis-Tulane Alumni Chair in Diabetes, and Chief of the Section of Endocrinology at Tulane University Medical Center in New Orleans, LA

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study was the first large outcomes-based clinical trial designed to assess the role of peroxisome proliferator-activated receptor (PPAR) agonists in the prevention of cardiovascular events in type 2 diabetes. Specifically, PROactive examined the effect of pioglitazone on macrovascular mortality and morbidity in 5238 patients with type 2 diabetes, A1C levels >6.5%, and evidence of cardiovascular disease (CVD). To be included, participants also had to be between 35 and 75 years of age (Table). In addition to existing therapy, patients were randomly assigned to receive either placebo or pioglitazone, which was titrated from an initial dose of 15 mg to a maximum of 45 mg, subject to tolerability.¹

Study results showed that 514 of 2605 pioglitazone patients and 572 of 2633 placebo patients reached the primary composite

end point, consisting of all-cause mortality, nonfatal MI (including silent MI), stroke, major leg amputation, acute coronary syndrome (ACS), cardiac intervention, or leg revascularization. This corresponded to a 10% risk reduction for the pioglitazone group, a level of improvement that was not statistically significant ($P=0.095$). The number of patients who reached the secondary composite end point, which consisted of all-cause mortality, nonfatal MI (excluding silent MI), or stroke, was 301 of 2605 pioglitazone patients and 358 of 2633 placebo patients. This represented a statistically significant 16% risk reduction among patients taking pioglitazone ($P=0.027$) (Figure).¹

Additional, placebo-adjusted results for pioglitazone recipients included a 0.5% decrease in A1C levels ($P<0.0001$), an 8.9% increase in HDL cholesterol levels ($P<0.0001$), a 5.3% reduction in LDL/HDL ratio ($P<0.0001$), a 13.2% decrease in triglycerides ($P<0.0001$), and a 2.3% increase in LDL cholesterol ($P=0.003$). Although the number of congestive heart failure (CHF) cases requiring hospitalization was higher among pioglitazone patients (6.0% vs 4.0%, $P=0.007$), the incidence of fatal heart failure did not increase. Peripheral edema, pneumonia, and nonserious hypoglycemia also were increased with pioglitazone.¹

Since its publication, PROactive has been criticized for a number of flaws in its design, methodology, and conclusions. For example, the failure to include silent MI and CHF in the secondary end point has been identified as a potential source of “interpretation” bias; inclusion of these end points would have caused the secondary end point to be statistically insignificant.

The decision to administer a 45-mg maximum daily dose of pioglitazone also has been questioned. This dose is the maximum approved dose, although many clinicians

It may be necessary to look beyond the “headline” results...before making decisions on the widespread translation of the trial results to clinical practice.

use lower doses of the drug in combination with insulin to avoid such adverse effects as edema and weight gain.² Given that CHF risk is increased when higher doses of pioglitazone and insulin are combined, it is worth considering whether the observed CHF incidence would have been improved with a 30-mg maximum daily pioglitazone dose. However, it is not clear if the macrovascular benefit seen with pioglitazone would have been the same at lower doses.

Other potential limitations of the PROactive study included omission of the secondary end point definition from the initial design publication, and significant end-of-study differences between the experimental and control groups, particularly for glycemic control (mean A1C levels of 6.9% vs 7.6% for the pioglitazone and placebo groups, respectively).^{1,3} According to the PROactive protocol, both the placebo and

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TABLE. PROactive Study: Criteria for Admission

Participants were required to have evidence of substantial macrovascular disease, with at least one prior CVD event:

- (1) MI, stroke, percutaneous coronary intervention, or coronary artery bypass graft at least 6 months before enrollment
- (2) Acute coronary syndrome at least 3 months prior to enrollment
- (3) Objective evidence of coronary artery disease
- (4) Symptomatic peripheral arterial occlusive disease

Dormandy JA, et al, on behalf of the PROactive investigators. *Lancet*. 2005; 366:1279-1289.

The PROactive Study

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pioglitazone groups should have been treated to meet current goals for metabolic control, including glycemic control.³ If that goal had been achieved, any reduction in end points could then be attributed to treatment with pioglitazone rather than to variations in glycemic control. Unfortunately, this precondition was not met. Furthermore, the use of drugs to prevent CVD, such as statins, was suboptimal in the trial overall.

In light of concerns expressed about the PROactive study, it is important for the diabetes community to carefully scrutinize future clinical trial designs, execution, and outcomes analyses. To ensure that the con-

clusions being drawn are compatible with the design and statistical power of the study, this should include particular consideration of primary versus secondary outcomes and subgroup analyses. In an era of declining numbers of absolute events (owing to the availability of multiple, effective therapies), such issues are now relevant for most trials evaluating cardiovascular outcomes.⁴

For example, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (n=9795), which examined the effect of fibrate therapy on CVD in patients with type 2 diabetes, found that 256 of 4895 patients receiving fenofibrate and 288 of 4900 placebo patients reached the primary end point (first MI or coronary heart disease death), corresponding to a statistically insignificant 11% risk

reduction ($P=0.16$). However, 612 of 4895 fenofibrate patients and 683 of 4900 placebo patients reached the secondary end point (total CVD events), resulting in a significant 11% reduction in the fenofibrate group ($P=0.035$). In this case, the observed benefits of fenofibrate were less than expected as a result of significantly higher average rates of statin use in the placebo group (17%) compared with the fenofibrate group (8%) ($P<0.0001$).⁵

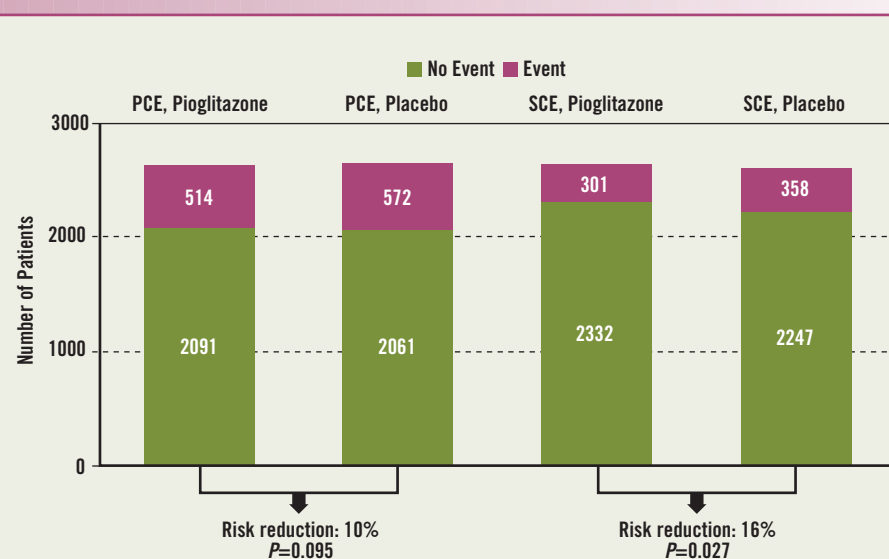
Discrepancies such as these, which may compromise the accuracy of a clinical study, need to be identified and eliminated whenever possible. It also may be necessary to pre-specify therapy in control groups. Furthermore, once clinical trial data have been published, these discrepancies need to be addressed candidly in open forums, much like the PROactive study has been discussed. It may be necessary to look beyond the “headline” results and the study abstract, and to examine the details of the patient population and the study outcomes before making decisions on the widespread translation of the trial results to clinical practice.

In spite of its limitations, PROactive is the first clinical trial to provide evidence of the cardiovascular benefits associated with pioglitazone use in patients with type 2 diabetes. Although its findings are not conclusive, PROactive offers support for the theory that treating insulin resistance reduces the risk of MI, stroke, and even death in patients with type 2 diabetes. Further research is necessary to validate and better understand the PROactive results. ■

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FIGURE. PROactive Study: Primary and Secondary End Point Events at 3 Years



PCE = Primary composite end point, consisting of:

- All-cause mortality
- Nonfatal myocardial infarction (including silent MI)
- Stroke
- Acute coronary syndrome
- Endovascular or surgical intervention in the coronary or leg arteries
- Amputation above the ankle

SCE = Secondary composite end point, consisting of:

- All-cause mortality
- Nonfatal myocardial infarction (not including silent MI)
- Stroke

Dormandy JA, et al, on behalf of the PROactive investigators. *Lancet*. 2005;366:1279-1289.

CME Post-test

To receive CME credit for having read this newsletter, choose the single best answer to each of the questions below. Write your answers in the corresponding blanks on the following page.

- 1 Which of the following statements accurately describes insulin and oral antihyperglycemic drug use patterns in the US?
 - A. Oral antihyperglycemic drug use has increased in the past decade
 - B. Insulin use has increased in the past decade
 - C. Insulin use has remained relatively stable in the past decade
 - D. Both A and C

- 2 What is the current American Diabetes Association (ADA) A1C target goal?
 - A. <6.5%
 - B. <7%
 - C. <7%, with a goal for individual patients of <6%
 - D. <8%

- 3 Which of the following statements regarding the concept of clinical inertia are true?
 - A. Research indicates that clinical inertia is not a substantial problem in type 2 diabetes management
 - B. In type 2 diabetes, clinical inertia represents the time that elapses between treatment failure and the restoration of normoglycemia
 - C. Research indicates that, due to clinical inertia, patients with type 2 diabetes may spend years with elevated A1C targets
 - D. Both B and C

- 4 Which of the following statements accurately describes current research findings on exogenous insulin use and safety?
 - A. The early use of insulin in type 2 diabetes may promote beta cell "rest"
 - B. The early, intensive use of insulin in type 1 diabetes appears to confer no long-term cardiovascular benefits
 - C. Compared to oral antihyperglycemic agents, insulin is less effective at lowering elevated A1C levels
 - D. The newer insulin analogies (ie, glargine, detemir) do not appear to lower hypoglycemia risk compared to older insulins (ie, NPH)

- 5 Which of the following have been cited as reasons why patients avoid transitioning to insulin therapy?
 - A. Fear of needles and/or injections
 - B. Fear that the need for insulin indicates that their health has worsened beyond repair
 - C. The perception that insulin is not an effective therapy
 - D. All of the above

- 6 Which of the following oral antihyperglycemic drugs appear to exert a cardioprotective effect?
 - A. Metformin
 - B. Pioglitazone
 - C. Neither A nor B
 - D. Both A and B

- 7 Please indicate whether the following statement is true or false: "Current research indicates that intensive in-hospital glycemic control following myocardial infarction (MI) improves clinical outcomes."
 - A. True
 - B. False

- 8 Which of the following statements regarding the PROactive trial is true?
 - A. The PROactive trial failed to meet its primary end point
 - B. The PROactive trial met its primary end point
 - C. The PROactive trial met its secondary end point
 - D. Both B and C

- 9 Which of the following have been noted as potential methodological flaws in the PROactive trial?
 - A. The administration of a pioglitazone dose not currently approved for use in combination therapy
 - B. The overuse of statin drugs in both trial arms
 - C. The failure to include silent MI and congestive heart failure in the secondary end point
 - D. Both A and C

- 10 Based on the findings of the PROactive study, please indicate whether the following statement is true or false: "PROactive provided clinical evidence that pioglitazone may confer cardiovascular benefits in patients with type 2 diabetes."
 - A. True
 - B. False

Insulin IDEAS

Newsletter Series Vol 1 No 1 ■ Clinical Update: Type 2 Diabetes Management ■ Released: June 2006

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Strongly agree Agree Disagree Strongly disagree

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Strongly agree Agree Disagree Strongly disagree Not applicable

4. **The educational activity will result in a change in my practice behavior.**

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Strongly agree Agree Disagree Strongly disagree

6. **What new information did you learn during this program?** _____

7. **Recommendations for topics of future presentations:** _____

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The Dual Role of Diabetes Therapy

continued from page 6

with IGT ($P=0.03$).²⁰ Thus, this class of drugs may offer a CVD prevention benefit for patients with type 2 diabetes.

Conclusion

Despite significant treatment advances, patients with type 2 diabetes continue to be at high risk for CVD. While blood glucose lowering clearly decreases CVD events, nonglycemic factors appear to also play an important role. Consideration of the specific beneficial effects of different diabetes drugs, combined with an understanding of which patient groups might benefit from a specific drug, will assist all physicians caring for patients with diabetes.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and A Diabetes Outcome Progression Trial (ADOPT) currently are testing the hypothesis that tighter blood glucose control and lower A1C targets may provide even greater CVD risk reduction benefits, and additional studies exploring the nonglycemic effects of insulin, metformin, TZDs, and alpha-glucosidase inhibitors will improve physicians' ability to implement a more individualized approach to type 2 diabetes therapy.^{21,22} ■

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About this Program

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glucose levels are not adequately controlled with oral agents. The course will explore the:

- Progressive loss of beta cell function
- Role of optimal glucose control in improving long-term outcomes
- Relative contributions of fasting and postprandial glucose levels to overall glycemic burden
- Importance of rapid advancement of therapy, including early use of insulin

Course 2: Use of Insulin to Achieve Optimal Glucose Control portrays the case of a man who, despite the use of 2 oral agents and basal

insulin, does not have optimal glucose control.

The course will investigate the:

- Role of insulin in achieving metabolic control and decreasing the vascular sequelae of type 2 diabetes
- Data suggesting that early insulin can slow or reverse disease progression
- Rationale for insulin therapy directed at both fasting and postprandial glycemic burden
- Options for addressing an individual patient's physiologic needs
- Emerging options for insulin therapy

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