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Point: Recent Long-Term Clinical Studies Support an Enhanced Role for Thiazolidinediones in the Management of Type 2 Diabetes

The treatment options for type 2 diabetes were for many years limited to sulfonylureas, metformin, and insulin. However, in the last decade or so, a number of new oral and injectable agents have been introduced including the thiazolidinediones, incretin-related compounds, and "designer" insulins. Despite these additions to practitioners' armamentarium, attainment of optimal glucose control has remained largely elusive, in large part because type 2 diabetes is a progressive disease and health care professionals have failed to initiate combination therapy, including insulin, in a timely fashion. With near-normoglycemia treatment targets, the approach to glycemic management currently being advocated by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the Canadian Diabetes Association (CDA) includes earlier commencement of treatment and more aggressive use of combination therapy (1,2). With few exceptions, most of these therapeutic recommendations are based on relatively short-term studies and expert opinion, as there are few long-term, head-to-head comparisons that provide definitive evidence.

Impact of the UK Prospective Diabetes Study and the Diabetes Control and Complications Trial

The UK Prospective Diabetes Study (UKPDS) helped fashion the current approach to diabetes management. This long-term study reported in 1998 and demonstrated that improved glucose control is associated with a reduced risk of microvascular complications (3,4). Further, it suggested that none of the therapies used in the study—sulfonylureas, metformin, and insulin—were able to slow the progressive nature of type 2 diabetes. Thus, over the course of more than 10 years, glycemic control deteriorated in all treatment arms at a rate that paralleled that in the cohort that received the conventional lifestyle intervention. At the time this landmark study was undertaken, the recommendations for glucose control differed markedly from those of today, so that "rescue" therapy for participants randomized to the conventional treatment arm was only instituted at a fasting plasma glucose level of 15 mmol/l (270 mg/dl).

The UKPDS confirmed the findings of the Diabetes Control and Complications Trial (DCCT) in patients with type 2 diabetes; namely, glucose control is critically important in preventing the microvascular complications of diabetes. In addition, the UKPDS underscored the realization that loss of β-cell function is characteristic of type 2 diabetes, and slowing this loss could potentially delay diabetes and its complications. As a result, a number of major clinical trials were spawned. These included four large studies that systematically asked whether lifestyle, metformin, acarbose, or the thiazolidinediones troglitazone and rosiglitazone can slow or even prevent the development of type 2 diabetes in individuals at increased risk (5–9). They clearly showed it is possible to slow the development of diabetes with lifestyle and that the thiazolidinediones were more effective then either metformin or acarbose. Further, the recognition that the insulin-sensitizing effect of the thiazolidinediones could decrease β-cell secretory demand led to the logical question whether these agents would reduce the loss of β-cell function and thereby provide more durable control of glycemia. To answer this question, A Diabetes Outcome Progression Trial (ADOPT) was undertaken (10).

What were the results of ADOPT and what has it taught us?

ADOPT, by comparing metformin, glyburide, and rosiglitazone in a large glycemia outcome study, has provided important new evidence to help guide our choices of therapy. In a cohort of over 4,000 recently diagnosed, drug-naïve, type 2 diabetic subjects, rosiglitazone reduced the need for the addition of a second agent by 32% compared with metformin and by 63% versus glyburide (11). At the time ADOPT was designed, the ADA was recommending addition of medication when fasting glucose reached 10 mmol/l (180 mg/dl) (12), and this therefore formed the basis for the choice of this glucose level for the primary outcome. While the choice of this threshold has been criticized based on today's targets (13), the robustness of the ADOPT outcome in relation to current clinical practice recommendations was demonstrated by the similar relative effectiveness of the three agents when the prespecified secondary outcomes, namely fasting glucose 7.8 mmol/l (140 mg/dl) and glycated hemoglobin 7% (11), were examined. ADOPT also indicated that the differences in outcome were related to the differing effects of the medications on β-cell function and insulin sensitivity. As in the UKPDS, glyburide increased β-cell function, but this effect was rapidly lost as function declined at 6.1% per year compared with 3.1 and 2.0% annually for metformin and rosiglitazone, respectively. Rosiglitazone and metformin also improved insulin sensitivity with greater effect than rosiglitazone, while glyburide had no such benefit.

ADOPT once again taught us that use of these medications is not "free." The well-recognized adverse events of weight gain and edema occurred with rosiglitazone, unpleasant gastrointestinal effects with metformin, and weight gain along with hypoglycemia with glyburide. In addition, rosiglitazone was linked to an increased risk of upper- and lower-extremity fractures in women. Of interest, a recent report indicated that thiazolidinediones may reduce bone mass (14). Somewhat unexpectedly, the reported adverse cardiovascular event of congestive heart failure did not differ in subjects receiving rosiglitazone or metformin, yet the event rates for these two parameters were lower in those on glyburide.

Thus, ADOPT has clearly demonstrated for the first time that the progression of hyperglycemia in type 2 diabetes can be slowed. Clearly the magnitude of this effect is of clinical importance, particularly when comparing rosiglitazone to glyburide.

What have we learned from other recent, long-term studies in type 2 diabetes?

The realization that there is a long latent period during which individuals transition from normal glucose tolerance to type 2 diabetes prompted the undertaking of long-term studies focused on preventing the progression from states of impaired glucose metabolism (pre-diabetes) to diabetes. These studies have demonstrated variable effectiveness of lifestyle intervention, metformin, acarbose, orlistat, and the thiazolidinediones in reducing the development of diabetes. The thiazolidinedione troglitazone proved effective in women with a history of gestational diabetes (15) and in subjects with impaired glucose tolerance (8); however, both these trials were prematurely discontinued because of the hepatic toxicity of troglitazone, which resulted in its withdrawal from the market. More recently, the results of the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) Trial (9) were announced and demonstrated that rosiglitazone was also effective and reduced the rate of progression to diabetes by 60%, a risk reduction similar to that seen with lifestyle in both the Diabetes Prevention Program (DPP) (6) and the Finnish Diabetes Study (5) and greater than reported with metformin in the DPP (6), acarbose in the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) program (7), and orlistat in the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study (16).

In spite of their ability to lower plasma glucose, the thiazolidinediones have not achieved wide-ranging acceptance, in part because of the weight gain and fluid retention observed with these agents. With these unwanted effects has also come the observation of an increased incidence of congestive heart failure, especially in those also using insulin or sulfonylureas (17). While the presentation of heart failure with thiazolidinediones appears to differ from that typically observed in individuals with type 2 diabetes (18), the long-term implications of an episode of cardiac decompensation as a consequence of fluid overload remain unknown. On the flip side, there are data suggesting that thiazolidinediones may be beneficial in reducing cardiovascular disease. Most powerful, but yet not conclusive, were the findings of the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) Study (19). This large study in individuals with established type 2 diabetes and cardiovascular disease was undertaken to determine whether pioglitazone reduced macrovascular disease events; the composite primary outcome failed to reach clinical significance. However, the number of events for the more-focused composite secondary outcome (all cause mortality, myocardial infarction, and stroke) was significantly reduced. Despite these potential benefits on cardiovascular outcomes, fluid retention and congestive heart failure were significantly more prevalent in those receiving pioglitazone in the PROACTIVE Study (19). A similar observation of an increase in heart failure was made with rosiglitazone in the DREAM Trial (9), but this was not observed with troglitazone in the DPP, possibly because the patient years of exposure was less (8), or in ADOPT, where the rate of heart failure assessed by independent cardiologists (unlike the investigator-reported adverse events of heart failure) was similar with rosiglitazone, metformin, and glyburide.

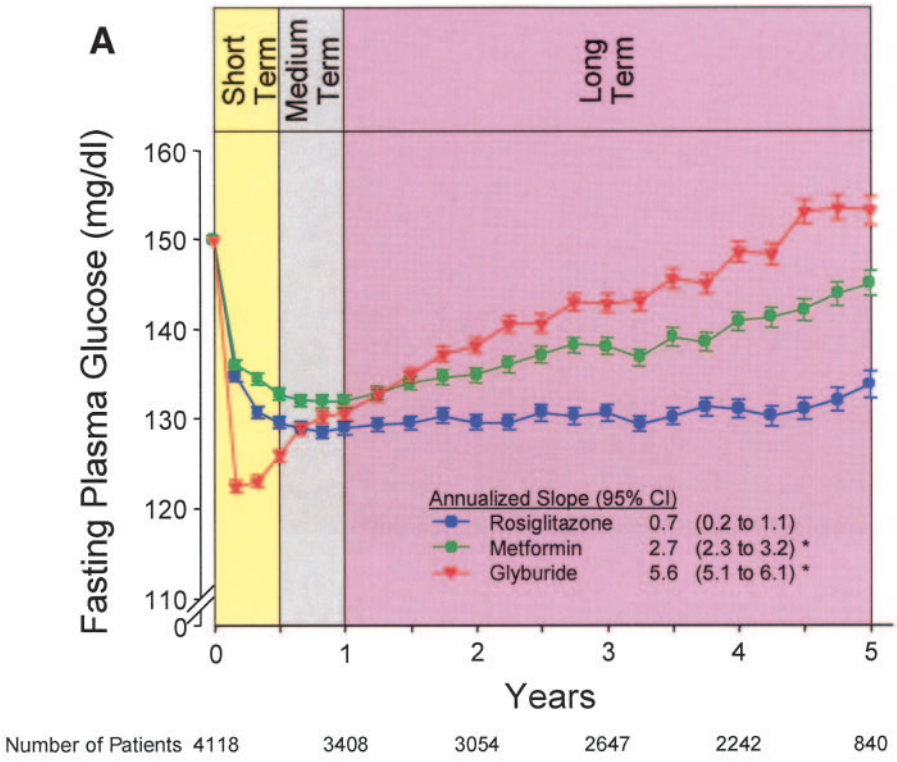
What have long-term studies in diabetes taught us compared with short-term studies?

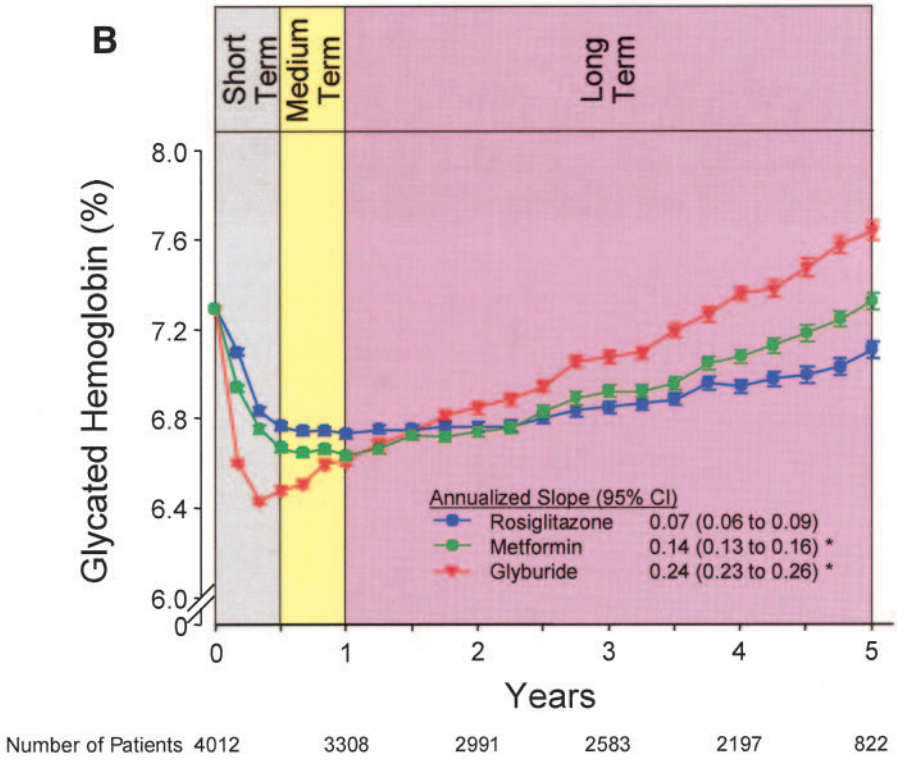
The results of research over the last decade have provided great insight and simultaneously raised new questions. This period has seen the development of a number of glucose-lowering compounds that have proven useful as therapeutic interventions in patients with type 2 diabetes. The proof of their ability to improve glycemic control, resulting in their registration, has been based on short-term studies, typically lasting 3 to 6 months. Further, their mechanisms of action have usually been determined using sophisticated approaches in small numbers of subjects treated for a limited period of time. And finally, their potential benefit beyond simply glucose control has been suggested using surrogate markers that frequently change rather rapidly or data from animal studies. While the value of these short-term studies is great, the necessity for long-term clinical outcome studies in type 2 diabetes has now been, more than ever, firmly established. To support this opinion we focus on glucose control, surrogate markers, and animal work.

Consider first glycemic control. The UKPDS and ADOPT both clearly highlighted the progressive nature of the type 2 diabetes disease process. The longitudinal data on glycemia in ADOPT are particularly instructive. In the first 6 months following institution of treatment, glyburide was clearly superior in improving glycemic control to both metformin and rosiglitazone (Fig. 1). At 2 years, glycated hemoglobin showed there was no clear glycemic benefit of any of the three agents. However, there can be no doubt that from a statistical and, more importantly, clinical standpoint, beyond 2 years glyburide proved to be inferior and progressively so.

Now turn to surrogate markers, and of great relevance, cardiovascular disease. All three thiazolidinediones have been shown irrefutably to rapidly reduce the progression of carotid intima-media thickness, with a recent report in a large number of subjects with type 2 diabetes showing this effect was different than that with the sulfonylurea glimepiride (20). This marker has been extensively utilized because it is believed to provide a good indication of not only what is happening to the cerebral vessels but also what is occurring at sites such as the coronary vasculature. Therefore, a reduction in cardiovascular events would be anticipated. Unfortunately, however, despite its long-term time frame, the PROACTIVE Study failed to conclusively demonstrate such dramatic effects on vascular outcomes. Thus, although still possible, it remains to be demonstrated that thiazolidinediones do in fact reduce cardiovascular disease. In addition, the significance of changes in intima-media thickness with these agents needs to be revisited.

Undoubtedly, studies in animals have been critical in understanding human type 2 diabetes and formulating approaches to its therapy. In fact, in some instances it is the work in animals that has redirected the usefulness of pharmacotherapeutics. A case in point is the dipeptidyl petidase-4 (DPP-4) inhibitors. The development of this class of compounds was driven by the belief that inhibiting this enzyme could alter the inflammatory response and prove beneficial in diseases completely unrelated to type 2 diabetes. It is only based on animal work that their glucose-lowering ability and subsequently their effect to slow degradation of the incretins was recognized (21). Further, animal studies have also demonstrated that the DPP-4 inhibitors and the incretin analogue exenatide reduce β-cell loss by decreasing apoptosis and fostering cell regeneration (21), thereby abating a





critical contributor to the loss of insulin release in type 2 diabetes (22). Does this effect occur in humans? We do not know and may never, as sampling pancreas in living subjects is clearly inappropriate. But some insight into this issue is critical if we are going to fully understand the potential value of these agents.

Have long-term clinical trials changed the treatment paradigm for type 2 diabetes, at least as far as glycemic control is concerned?

It is our conviction that the additional knowledge gained from recent long-term clinical trials suggests that modification of the latest recommendations of the ADA and EASD (1) may already be in order. It is now clear that metformin and the thiazolidinediones can slow progression of glycemia in individuals with impaired glucose tolerance and type 2 diabetes through their dual effects of enhancing insulin sensitivity and slowing β-cell function loss (8,11,15). On the other hand, sulfonylureas only affect the β-cells, improving secretion initially but not being able to sustain this effect, resulting in the progressive loss of glycemic control at a rate beyond that of either metformin or rosiglitazone (11). Further, there is an additional practical disadvantage to sulfonylurea use. With recommendations that pharmacological therapy be instituted earlier and with target glycated hemoglobin values that are lower, the risk of sulfonylurea-induced hypoglycemia is increased and therewith compliance will be more difficult. While clearly metformin and thiazolidinediones are themselves not without adverse effects, the troubling nature of these adverse effects

Figure 1—*Fasting plasma glucose* (A) *and glycated hemoglobin* (B) *over time according to treatment group assignment in ADOPT. The typical durations of short-, medium- and long-term clinical trials are indicated by the shaded areas and highlight the important differences in glucose control observed when studies vary in duration. The total number of patients included for each measurement at annual time points is indicated below each graph. Data are presented as means ± SE and the annualized rate of change (slope) from 0.5 to 5 years. *Significant differences between the rosiglitazone group and the other two treatment groups. For fasting plasma glucose, treatment differences (95% CI) at 4 years for rosiglitazone vs. metformin were −9.8 mg/dl (−12.6 to −7.0),* $P < 0.001$*, and for rosiglitazone vs. glyburide −17.4 mg/dl (−20.4 to −14.5),* $P < 0.001$*. For glycated hemoglobin, treatment differences for rosiglitazone vs. metformin were −0.13% (−0.22 to −0.05),* $P = 0.002$*, and for rosiglitazone vs. glyburide −0.42% (−0.50 to −0.33),* $P < 0.001$*. Adapted with permission in 2007 from ref. 11. (Copyright 2006 Massachusetts Medical Society. All rights reserved.)*

can be reduced when they are used at less than maximal doses and/or as low-dose combination therapies early in individuals with relatively moderate hyperglycemia.

Based on these observations, we agree with the recent recommendations that metformin be considered as first-line therapy for individuals with recently diagnosed diabetes in whom glycated hemoglobin levels are >7%. However, in contrast to these guidelines, we would advocate that the role of sulfonylureas should be supplanted by the thiazolidinediones. Thus, should metformin not be suitable as initial therapy or if use of dual agents is warranted, it would be reasonable to prescribe a thiazolidinedione instead of a sulfonylurea.

In considering these guidelines and the recent data, we also recognize that there is greater acceptance of early intervention with more than a single agent and that the natural history of the disease has not been well defined in the face of dual therapy, whether it is introduced early or late in the course of the disease. However, what is abundantly clear from short-term studies is that a number of combinations of agents that address different aspects of the pathophysiology are capable of effectively improving glucose control and frequently do so with smaller doses of each agent and less unwanted effects, although this is not always the case. Whether such effects can be sustained for longer periods of time requires data from additional clinical trials.

What have long-term clinical trials taught us about future research on therapeutics for type 2 diabetes?

To this the answer is relatively simple. Large clinical trials performed over a period of ≥3 years provide insight that short-term studies designed for registration of single or combinations of agents simply cannot. That is not to say that these shorter studies are not valuable, just that they have a different niche in informing us about diabetes therapeutics.

A case in point is the development of newer agents targeting the β-cell. This area of investigation is logical and important based on our understanding of the vital role of impaired insulin release in type 2 diabetes. Short-term improvement in β-cell function is associated with improved glycemic control. However, as practitioners, it is now critical that we know whether the glucagon-like peptide-1 analogues and DPP-4 inhibitors do or do not reproduce the findings regarding the loss of β-cell function observed with sulfonylureas. As mentioned, these newer agents clearly improve insulin release in humans by enhancing incretin action and have in animal studies also been shown to reduce cell death and enhance β-cell regeneration (21). Whether β-cell number increases in humans and/or a sustained improvement in β-cell function results are unknown and will not likely be discernable by short-term studies. We will ultimately require long-term clinical trial evidence of durability, and direct comparisons with other therapeutic agents would be particularly informative.

Conclusions

Evidence-based medicine has certainly contributed to a changing landscape in clinical practice, and large, long-term clinical trials have added to this process. In the area of diabetes, that which we have learned from clinical studies reported over the last decade has been tremendous, and there is no doubt that as more data from these trials are reported, we will gain greater insights. With this additional information we have also been provided the opportunity to develop and amend clinical guidelines, and it is our conviction that the time has arrived for us to take the evidence and reconsider the role of thiazolidinediones and sulfonylureas in the treatment of type 2 diabetes.

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NOTE ADDED IN PROOF

Since submission of this manuscript, the manufacturer of pioglitazone has reported that the use of this medication is also associated with an increased risk of fractures in women.

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