The Need for Glycemic Trials in Type 2 Diabetes

Carlos Abraira, MD, and William Duckworth, MD

The importance of glucose control in diabetes is firmly established. Numerous studies including the Diabetes Control and Complications Trial (DCCT), the U.K. Prospective Diabetes Study (UKPDS), and other smaller studies have shown a reduction in microvascular complications with improved glucose control. These studies have ended the argument about the benefits of lowering glucose levels in diabetes. The pendulum has swung decisively to glucose control.

Our current dilemma is: could the pendulum swing too far? Improved glucose control is beneficial, but how improved should control be? Should every patient strive for normal glucose? Is there a downside to intensive control? Does glucose control alone provide protection against all of the complications of diabetes? Is there a difference between the types of diabetes regarding the degree of optimal control?

Available data do not provide answers to most of these questions. Some of the answers, however, are blatantly obvious. A patient with advanced cancer or severe Alzheimer's disease should not be subjected to rigorous intensive glucose control. Most clinicians would support this conclusion. Thus, a one-size-fits-all recommendation for glucose control (hemoglobin A_{1c} [A1C] <6.5 or 7%) is not appropriate. Treatment goals must be individualized.

A separate issue, among many others, is the potential for the level of glucose control to have a different influence on complications in patients with type 1 versus type 2 diabetes. Patients with type 1 diabetes have a long period of hyper-glycemia, which increases the risk of hyperglycemia-associated complications. Patients with type 2 diabetes are at risk of complications resulting from hyperglycemia, but other factors may play an important role. Many individuals with type 2 diabetes also have an associated syndrome complex (the metabolic syndrome) including hypertension, dyslipidemia, insulin resistance, and obesity, which, along with aging, increases cardiovascular risks above and beyond the risks of hyperglycemia.

What Is Believed and What Is Known About Glycemia and Cardiovascular Complications

Cardiovascular morbidity and mortality are by far the most prevalent causes of excess suffering and economic burden in type 2 diabetes.[1] Compared to the very

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IN BRIEF

Glycemic control is a well-established treatment objective in diabetes care. However, the effectiveness and specific goals of glycemic control are not yet known for older type 2 diabetic patients with advanced complications and suboptimal response to current treatments. Therefore, current glycemic guidelines for such patients are variable. This article presents the rationale for ongoing long-term clinical trials to answer these questions and reviews the demonstrated effectiveness of hypertension and dyslipidemia control in reducing both microvascular and macrovascular complications.

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low risk of dying of microvascular disease, namely end-stage renal disease (ESRD), for a typical patient diagnosed at age 50–55, the mortality from cardiovascular causes is 40–70 times higher.[1,2]

Because diabetes is diagnosed and its control is assessed by blood glucose level, it is commonly believed that controlling glycemia is the cornerstone of diabetes treatment strategies to prevent cardiovascular disease. A recent publication of the American Diabetes Association (ADA)[3] confirms that this is a prevalent viewpoint. Of 900 primary care physicians queried in a 2002 report, a clear majority (65% of respondents) identified glycemic control as the most effective means of preventing cardiovascular disease, followed by hypertension in second place and lipid control in third place. At about the same time, the results of a meta-analysis of randomized clinical trials in type 2 diabetes indicated precisely the opposite conclusions.[4] The most effective way to prevent cardiovascular events is lipid control (106 people/year needed to treat), followed by hypertension control (157 people/year needed to treat), whereas glycemic intervention is nonsignificant (the confidence interval became meaningless because it extended into adverse results). The only trial offering significant benefit used an insulin infusion after myocardial infarction.[5] Similar infusions in patients without diabetes afforded comparable protection, so the benefit may not relate to glucose normalization.[6]

Clearly, there is a dissociation between known facts and physicians' beliefs. Lacking proof of a significant effect of intensification of glycemic con-

trol on cardiovascular outcomes, the epidemiological correlation between prevalent A1C results and cardiovascular outcomes is often presented as an indication that intensive control could similarly benefit these outcomes.[7] Not all epidemiological data establish this correlation.[8]

Glycemia, Blood Pressure, and Microangiopathies

The available evidence indicates that the most important reason to attain glycemic control in type 2 diabetes is the prevention of retinopathy, the main outcome in glycemic intervention trials. No large glycemic control trial has yet demonstrated an improvement in visual acuity or vision loss.

The UKPDS was the most important and longest-term trial in the treatment of type 2 diabetes (10–15 years of follow-up). In this study of newly diagnosed type 2 diabetic patients, the most important clinical outcome of glycemic intervention by sulfonylureas and insulin was a reduction of 3/1,000 patients/year on retinal photocoagulation.[9] There was no effect on visual acuity, renal failure, or cardiovascular events. A partial explanation of the limited benefit is the narrow A1C separation between the intensive and control arms (0.9%), both of which continuously rose in parallel more than 2% each from the beginning of the study.

It should be remembered that in adult patients with diabetes diagnosed later than 35 years of age, two-thirds of all vision loss is from nondiabetes causes.[10] Fifty to eighty percent of patients with type 2 diabetes have hypertension. In the UKPDS, even modest reduction in blood pressure, from 154/87 to 144/82 mmHg, was more than twice as effective as glycemic intervention in preventing the clinical outcomes of retinopathy. Unlike glycemic intervention, 12.5 years of blood pressure reduction was also effective in protecting visual acuity. It also reduced mortality and combined cardiovascular events.[11] What's more, independent of glycemic or blood pressure control, periodic ophthalmic examination and intervention as needed can prevent 90% of vision loss.[12]

Earlier estimates projecting for type 2 diabetes the glycemic benefits demonstrated in the DCCT for type 1 diabetes—estimates that did not consider the effect of blood pressure control or that of periodic eye examination and intervention—indicated that keeping A1C <11.5% would prevent 85% of lifetime risk of vision loss in a given population with type 2 diabetes. By simply keeping A1C <9%, about 98.8–99% of vision loss will be prevented, depending on the age at diagnosis, from 55 (about the peak prevalence of diagnosis of diabetes) to 75 years.[13] Likewise, even ignoring the protective effects of blood pressure control over progression of renal disease and the added benefit of using an angiotensin-converting enzyme inhibitor, the lifetime reduction in risk for ESRD by glucose lowering from an A1C of 9 to 7% is even smaller (about 0.3%).[13] These projections of modest clinical benefit from glycemic intervention were validated by the results of the UKPDS.

Current Guidelines

Thus, it might seem that recommended policies regarding blood pressure and lipid intervention and prevention of excessive glycemic deterioration would be an effective strategy not only to prevent cardiovascular disease but also to protect vision and renal function in the overwhelming majority of patients with type 2 diabetes. Consequently, the evidence-based current guidelines from the Department of Defense and Department of Veterans Affairs (VA) have as glycemic control goals A1C results <7, 8, or 9%, depending on life expectancy, degree of complications, or both.[14] The ADA's glycemic control goals indicate a target A1C of <7% for both type 1 and type 2 diabetes. (Until 2002, the ADA also recommended 8% as an action level for change of treatment.) These goals are attenuated in cases involving extremes of age, a patient's inability to carry out the advised treatment, or the presence of advanced complications.[15] The Diabetes Physician Recognition Program, another evidence-based program of the ADA, the VA, the National Committee for Quality Assurance, and other national professional associations, awards half of the 10 glycemic control points (5 out of 110 total possible points) to practices that keep 79% of patients at an A1C <9.5%. The overwhelming emphasis in point awards is given to general preventive care and blood pressure and lipid control.[16]

On the other hand, based on the same evidence used by the other advisory bodies, the American College of Endocrinology recommends an A1C goal of <6.5% for all patients.[17] This discrepancy illustrates the need for a clinical trial.

Treatment Options: Lifestyle Change and Oral Agents

There is little argument that prevention of obesity, adequate exercise, and treatment with insulin sensitizers (metformin or thiazolidinediones) delay the appearance of overt diabetes in patients at risk.[18] Once overt diabetes is manifested, on the basis of clinical trial evidence, it can now be reasonably expected that glycemic control with the addition of metformin for obese patients and sulfonylureas for all patients will not increase the risk for cardiovascular disease. Doubts that arose in the 1970s, after sulfonylurea treatment was linked to adverse cardiovascular events in the University Group Diabetes Program,[19] have now been put to rest. Sulfonylureas are beneficial in preventing microvascular disease.[9]

In the UKPDS, metformin was given as an initial agent to obese patients, a prospective randomized stratum. Metformin reduced total and cardiovascular mortality, not only compared to the control arm, but also compared to therapy with sulfonylurea or insulin.[20] This effect did not result from glycemic control, which was less effective with metformin than with sulfonylureas or insulin. Neither sulfonylureas nor metformin were

effective in preventing microvascular complications in the subgroup analyses of obese patients.

Paradoxically, the addition of metformin to sulfonylurea-treated patients did not demonstrate additional outcome advantages, but rather increased cardiovascular mortality by 96% compared to patients continuing on basal sulfonylureas.[20] These results have been repeatedly challenged on different grounds: it was a secondary randomization; the overall mortality in the combination therapy was still lower than the mortality of the overall UKPDS cohort; the risk profile of the obese population was higher than that of the full cohort; and epidemiological assessment of the use of the combination in the different treatment arms (but excluding the patients participating in the secondary randomization) did not confirm an increased risk with the sulfonylurea-metformin combination.

Prompted by the UKPDS results of the randomized study of this combination therapy, one assessment of a large Swedish population, corrected for cardiovascular risk factors, and data from a secondary intervention lipid trial in Israel also demonstrated an epidemiological correlation between the use of the sulfonylurea-metformin combination and higher mortality.[21,22] On the other hand, a more recent large epidemiological study did not reveal increased mortality with the use of this combination.[23] The ADA position statement on the implications of the UKPDS concludes, "If there is some specific mechanism of adverse interaction between metformin and sulfonylurea drugs, this can only be definitely determined in a new, appropriately designed, randomized, placebo-controlled trial."[24] We are not aware of new trials being conducted for this purpose.

Several new oral agents have become available in the past few years, offering variable glycemic management advantages, especially in combination with other oral therapies or insulin, but no long-term effects on clinical outcomes are yet available.

Insulin Treatment

Once type 2 diabetes progresses to the point where glycemic control goals are not met with lifestyle and oral agents, the addition or substitution of insulin is the only available option. Insulin use is expensive and cumbersome, demands preservation of self-injection and dose-adjustment skills in older and variably impaired patients, exposes patients to the nuisance of unavoidable increases in risk for mild and moderate hypoglycemia with associated cognitive and noncognitive psychological abnormalities,[25–29] may cause weight gain with the associated increase in cardiovascular risk, and carries the additional potential risks of hyperinsulinemia.[27] However, the UKPDS found no increase in cardiovascular risk with the initial use of insulin in newly diagnosed patients.

The only glycemic intervention trial to date involving patients with established, insulin-requiring type 2 diabetes no longer responsive to maximal oral sulfonylurea doses was the VA Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2 (VACSDM) Feasibility Trial. That trial of 153 patients sustained a glycemic separation (a difference in A1C results of 2.1%) exceeding that of other type 2 diabetes trials. The VACSDM Feasibility Trial showed a paradoxical trend of borderline significance between lower attained A1C results and new cardiovascular events.[28] One possible explanation for these results is that, unlike the UKPDS, the VACSDM Feasibility Trial studied older patients with longstanding diabetes requiring higher doses of insulin to achieve glycemic control and had a near-universal prevalence (84%) of cardiovascular abnormalities at baseline. Other reasons might be an "early worsening" effect (similar to that observed in microangiopathy) and/or destabilization of glycated products in vascular plaques by glucose lowering, or chance alone in such a small trial. The VACSDM study group advised that in treating such patients, target A1C results should not be <8% until such time as a properly

designed, full-sized glycemic control trial determines that intensive control to normalize glucose levels is beneficial.[28]

Current Trials

Two large trials are underway to address whether intensification of glycemic treatment aiming to normalize A1C results with current pharmacological therapies is beneficial, neutral, or conceivably even adverse in the prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, sponsored by the National Heart, Lung, and Blood Institute, will soon expand to its full patient cohort. This trial has been designed to randomize into two levels each of lipid control, blood pressure control and glycemic control, a large cohort of patients who are not yet treated with insulin but have cardiovascular abnormalities and are at heightened risk for new events.[29]

The VA Diabetes Trial (VADT), the full-sized trial that followed the VACSDM Feasibility Trial, began in December 2000, and its main treatment design is being published.[30] Briefly, like its predecessor, it incorporates poorly controlled, established type 2 diabetic patients who are nonresponsive to maximal doses of oral agents. A total of 1,760 men and women are being enrolled in 20 medical centers. The primary objective is to assess the effect of intensive glycemic treatment on combined major cardiovascular events (myocardial infarction, severe congestive heart failure, stroke, amputation, coronary intervention, and cardiovascular death). Other objectives are to assess the effects of treatment on microangiopathy and on costs and quality of life.

The VADT accrual period is 2 years, with a follow-up of 5–7 years. Subjects are being randomized to an intensive treatment or standard treatment arm with usual, improved glycemic control, and a separation in A1C results of at least 1.5% is to be maintained throughout the study. Both arms receive stepped therapy of glimepiride or metformin plus rosigli-

tazone, in addition to added insulin and other oral agents to achieve goals. Strict control of blood pressure and dyslipidemia, daily aspirin use, diet recommendations, and diabetes education are identical in both arms. Plasma fibrinogen, plasminogen activator inhibitor-1 lipids, renal function, and electrocardiograms are centrally measured and analyzed throughout the study. Stereo retinal photographs are obtained at entry and 5 years, and eye examinations are conducted yearly with interventions as needed.

The VADT standard treatment arm is projected to have median values similar to those of the intensive arm of the UKPDS in its last 5 years. (All UKPDS results were expressed in median, not mean, values.) The duration of diabetes diagnosis by that far into the UKPDS was equivalent to that of the VADT at entry. Thus, the VADT has started where the UKPDS left off. In the VADT, the first 1,091 patients enrolled have A1C results of 9.4 ± 1.6%, and their duration of diagnosis is 11 ± 8 years.

Expected Results in the VADT: Microangiopathy and Cardiovascular Disease

For all of the three main metabolic risk factors in diabetes—glycemia, hypertension, and dyslipidemia—the patients in the VADT standard arm are receiving better treatment than under current care. It is expected that the clinical outcomes of microangiopathy (visual acuity, renal failure, and symptomatic neuropathy) will not differ between the intensive and standard treatment arms. Furthermore, given the protective effect of hypertension control on renal and visual[11] function and the benefit of lipid control in renal function,[31] it is likely that the glycemic differences in this 6-year trial will not result in between-group differences in the less severe clinical outcomes of retinal photocoagulation, gross proteinuria, or neuropathic findings. Careful monitoring for changes in microalbuminuria, neuropathy, or retinal photographic findings will be conducted throughout.

This raises an important question: how could a trial of glycemic intervention be able to demonstrate an effect on cardiovascular events if few or no clinical changes are expected in microangiopathies, the most uniformly significant outcome of all studies of glycemic intervention?

As already addressed above, the greatest progression in microangiopathy outcomes occurs at increasingly high to very high A1C deterioration (9.5% or higher). The differences when A1C results are <8.5%, in absolute terms, are narrow enough that it has been repeatedly proposed that a threshold for the glycemic damage to renal and retinal complications may occur with A1C results between 8 and 8.5%.[32,33] More recently, the DCCT and UKPDS both determined continuous changes all the way down to A1C results just above normal, thus proving that there is no such threshold. Nonetheless, at A1C results <8.5%, the lifetime additional advantages of glucose lowering are quantitatively minimal and, in patients who need insulin, have to be balanced against the unavoidable and rapid progression of mild and moderate hypoglycemic events. On the other hand, for myocardial infarction, there is epidemiological evidence suggesting that risk begins at the upper limit of normal glycemia and rises until reaching a plateau when A1C results are >9.5%.[7] This major cardiovascular event alone is about three times more frequent than the microvascular events at this relatively low A1C range.

In conclusion, the VADT is positioned, by ensuring optimal blood pressure and lipid control in both arms and preventing glucose deterioration in the control arm, to demonstrate the putative effect of intensive glycemic intervention on cardiovascular outcomes, while protecting against an excess of adverse clinical microangiopathy outcomes in either arm. This trial may answer one of the most important questions in the treatment of diabetes.[34]

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Carlos Abraira, MD, is a professor of medicine at the University of Miami VA Medical Center in Miami, Fla. William Duckworth, MD, is director of diabetes research at the VA Medical Center, a research professor at Arizona State University, and a professor of clinical medicine at the University of Arizona, Phoenix, campus in Phoenix, Ariz. The authors are co-chairmen of the VA Diabetes Trial.