The control of glycated hemoglobin (HbA1c) levels is key to the successful treatment of patients with diabetes mellitus (T2DM). Glycemic control is a cornerstone for reducing end-organ disease, and HbA1c is the benchmark for defining glucose control over long durations. The American Diabetes Association (ADA) recommends an HbA1c level of less than 7% in most individuals—and lower in selected individuals if it can be achieved without hypoglycemic events.1 The American Association of Clinical Endocrinologists (AACE) suggests an HbA1c level of less than 6.5% as the treatment goal.2

Data from clinical trials published in 2008 have prompted reevaluations of these recommendations. It would not be surprising to see HbA1c targets redefined primarily in terms of each patient’s particular health status. For example, should an HbA1c level of 6% or lower be the goal for teenagers and young adults with T1DM and T2DM? Is an HbA1c level of less than 7% appropriate for healthy adults in middle age, and is an HbA1c target of 7% or lower—if possible without hyperglycemia—appropriate for robust geriatric patients?3

Perhaps an HbA1c level of 8% or lower is appropriate for patients with long-standing cardiovascular disease (CVD) and for those facing end-of-life issues.

The HbA1c metric is a surrogate marker for glycemic control in patients. Much emphasis is placed on this measurement because most clinical trial results and epidemiologic data demonstrate that glycemic control is a cornerstone for reducing end-organ disease. In addition, HbA1c is the benchmark for defining glucose control over the duration of a clinical study. Although data supporting tight glycemic control are much stronger for microvascular risk reduction3-6 than for macrovascular risk reduction,7-10 no data suggest that poor glycemic control is beneficial.

The present article reviews available information from clinical trials regarding the benefits of tight glycemic control in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). He notes that published data support the use of tight glucose control for reducing risks of retinopathy, nephropathy, and neuropathy in both patients with T1DM and patients with T2DM. He also notes that early aggressive insulin management of younger individuals with T1DM led to reductions in the incidence of myocardial infarction (MI), stroke, and death. However, published data do not clearly support benefits of tight glucose control for the prevention of cardiovascular events in older patients with long-standing T2DM.

The author also reviews recommended treatments for achieving and maintaining glycemic control in patients. He concludes that the most successful treatment requires that physicians encourage patients to actively participate in the management of their own disease, and that physicians provide patients with opportunities to learn the cornerstones of effective therapy.
Microvascular Disease

The Diabetes Control and Complications Trial (DCCT), conducted from 1983 to 1993, involved 1441 patients between the ages of 13 and 39 years with T1DM. The average HbA1c level attained by patients in the intensive therapy group (ie, three or more insulin injections daily) was 7.4%, compared with 9.1% in the standard treatment group (ie, one to two insulin injections daily). These results suggested that intensive therapy was superior to standard treatment.

Over 5 years in the DCCT, the risk for development of neuropathy was reduced by 69% (P<.001). Over 9 years in the DCCT, the risk for nephropathy was reduced by 34% (P<.01) and that for retinopathy was diminished by 76% (P<.001). However, no statistically significant benefit was found in terms of risk reduction for macrovascular disease.

Subsequently, 93% of the participants in the DCCT were followed up in the observational Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study until as late as 2005, for an average of 17 years of follow-up. Because the DCCT/EDIC was an observational study, subsequent care was given to patients by their own healthcare providers. Over the course of follow-up treatment, patients who had received intensive treatment and those who had received standard treatment converged at an average HbA1c level of approximately 8%. However, results of the DCCT/EDIC also showed that participants who achieved tight glucose control in the original DCCT had a 42% decrease in all CVD events and a 57% decrease in nonfatal myocardial infarctions (MIs), stroke, and death after almost two decades of intensive treatment (P<.001). Researchers concluded that early aggressive control of T1DM had the long-term benefit of reduced macrovascular disease.

The benefits of tight glucose control have also been demonstrated in individuals with T2DM. The landmark studies conducted by the United Kingdom Prospective Diabetes Study (UKPDS) group demonstrated that over 10 years, management with a sulfonylurea or insulin or with metformin resulted in risk reductions of 37% in microvascular disease and 43% in peripheral vascular disease per each 1% decrease in HbA1c level (P<.001). Obvious trends in reduced risks of congestive heart failure (16%), MI (14%), and stroke (12%)—though not statistically significant—were also observed in the UKPDS.

Researchers at Kumamoto University School of Medicine in Japan focused on comparing patients with T2DM who were managed to achieve an average HbA1c level of 7.2% versus those managed to achieve an average HbA1c level of 9.4% over 6 years. Although this was a small trial (N=110), the results were significant, with the incidence of retinopathy reduced by 69% and that of nephropathy by 70% (P<.001).

Macronutritional Disease

Based on the results from the DCCT, UKPDS, and the Kumamoto University study, it appears clear that tight control of glucose levels reduced the risk of microvascular disease in patients with T1DM and those with T2DM. In addition, the DCCT/EDIC results suggest that early implementation of tight glucose control reduced the risk of macrovascular disease in patients with T1DM. However, the question remains open regarding the value of HbA1c reduction as an intervention for decreasing macrovascular disease in patients with T2DM. Hence, several large long-term studies have specifically addressed the issue of glucose control in prevention of CVD events. These studies include the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, and the Veterans Affairs Diabetes Trial (VADT).

The ACCORD study, sponsored by the National Institutes of Health, included approximately 10,000 patients with T2DM. The average age of the participants was about 60 years (range, 40-79 years). All participants had long-standing diabetes mellitus, a history of at least one CVD event, or risk factors for CVD. The primary hypothesis of the ACCORD researchers was to determine if intensive treatment to lower HbA1c levels to less than 6% would reduce the rate of CVD events (ie, MI, stroke, or death) more so than standard treatment to achieve an HbA1c level of 7% to 7.9% in the setting of controlled blood pressure and lipid levels. Those patients in the intensive treatment arm of the trial had an average HbA1c reduction from 8.1% to 6.4% over 12 months. By contrast, those patients in the standard treatment arm had an average HbA1c reduction from 8.1% to 7.5% over this period.

The ACCORD study was stopped early because excess death was detected in the intensive treatment group—there were 14 deaths per 1000 patient-years with the intensive therapy regimen versus 11 deaths per 1000 patient-years with the standard therapy regimen. The cause of the observed excess death remains unknown. Hypoglycemia with intensive treatment may not be the cause, because the death rate from hypoglycemia was similar in both treatment groups.

Moreover, it is important to keep in mind that the death rate from MI in untreated individuals with diabetes mellitus is approximately 5% to 6% per year—that is, about 50 to 60 deaths per 1000 patients per year. By contrast, the death rates observed in the ACCORD study (11-14 deaths per 1000 patient-years) indicate that either intensive or standard treatment to lower HbA1c levels is very effective. There was a more than fourfold decrease in the death rate of ACCORD participants in whom HbA1c levels were reduced to the range of 6.4% to 7.5%? Findings and conclusions from the ACCORD study are presented in Figure 1.

Of course, a confounding variable in interpreting the ACCORD results is that trial participants also had their blood pressure and lipid levels managed to goal—which contributed to the observed beneficial outcomes. Thus, it remains unclear from the ACCORD study if tight glycemic control in the setting of older individuals (ACCORD age range, 40-79 years) with diabetes mellitus and CVD is an appropriate intervention. It is possible that when other CVD risk factors are well controlled, the roughly 1% difference in HbA1c levels observed between the intensive and standard treatment
The ADVANCE study was about 62 years. The average age of participants in the inclusion criteria was among the 11,000 people with T2DM. The S10 JAOA Supplement 1 Vol 109 No 5 May 2009 treatment group had been targeted to 9%, which is about the national HbA1c target of standard treatment was <6%. The glycosylated hemoglobin target of intensive treatment was 7%-7.9%.

However, as previously noted, this lack of perceived benefit may be the result of the small difference in HbA1c levels observed between the intensive and standard treatment groups. The VADT was a prospective, randomized, multicenter, open-label study conducted over 5.6 years. The goal of the VADT researchers was to determine if there was benefit in reducing HbA1c levels by at least 1.5% in patients with long-standing diabetes mellitus (ie, average duration of approximately 11 years). The average age of the participants was 60.4 years, and 40% of the participants had a history of at least one previous CVD event. Patients in the intensive treatment group of the VADT achieved an average HbA1c level of 6.9%, while patients in the standard treatment group achieved an average HbA1c level of 8.4%. Overall, no differences in microvascular or macrovascular outcomes were found between the two groups—except for some progression of microalbuminuria in the standard treatment group. However, a subgroup analysis showed that participants who had diabetes mellitus for less than 12 years had fewer CVD events while using intensive therapy.

Thus, what can be gleaned so far from the present review of clinical data? Published data support the benefits of tight glycemic control for reducing risks of retinopathy, nephropathy, and neuropathy in patients with T1DM and those with T2DM. Data from the DCCT/EDIC study support early aggressive insulin management of younger people with T1DM (age <40 years), showing that 17 years after treatment initiation, the incidence rates of MI, stroke, and death were reduced in these individuals. However, published data do not support any benefit of tight glycemic control for the prevention of CVD events in older patients with long-standing T2DM. However, as previously indicated, metformin is generally recommended as the initial pharmacologic agent. The DPP-IV inhibitor sitagliptin phosphate is also an appropriate initial choice because it is highly effective in controlling HbA1c levels and has a good tolerability profile.

**Steps to Achieve Glucose Goals**

Given the available data, there is no question that glycemic control must be attained in patients with diabetes mellitus for treatment to be effective. The ADA, the AACE, and the Texas Diabetes Council (TDC) recommendations for achieving this goal are safe and congruent with the interventional and observational data. The following paragraphs discuss four main steps for meeting these recommendations. In addition, the TDC’s algorithm aids making decisions on glycemic control for patients with T2DM. Step 1 is to initiate treatment for patients with diabetes mellitus. Figure 2 shows current standard treatments for patients with T2DM and the expected results of each treatment. Diet and exercise remains the cornerstone of diabetes mellitus management, because these factors reduce insulin resistance in patients. Diet and exercise—with a focus on a weight loss of 5% to 10%—is recommended for all patients with impaired fasting glucose levels or impaired glucose tolerance. Prescribing metformin is an option if the patient’s HbA1c level is more than 6% or if the patient has other risk factors for diabetes mellitus, such as hypertension, low levels of high-density lipoprotein cholesterol, or impaired fasting glucose levels plus impaired glucose tolerance. When diabetes mellitus is diagnosed, the initial intervention includes the cornerstones of therapy, in addition to self-monitoring of blood glucose levels and initiation of metformin oral therapy.

Selecting the initial drug therapy for a patient with T2DM is a straightforward process. Metformin, a thiazolidinedione (TZD), a dipeptidyl peptidase IV (DPP-IV) inhibitor, an α-glucosidase inhibitor (AIG), one of the glinides, and a sulfonylurea are all appropriate choices. However, as previously indicated, metformin is generally recommended as the initial pharmacologic agent. The DPP-IV inhibitor sitagliptin phosphate is also an appropriate initial choice because it is highly effective in controlling HbA1c levels and has a good tolerability profile.

**Figure 1.** Findings and conclusions from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.*7,11* The glycosylated hemoglobin target of standard treatment was <6%. The glycosylated hemoglobin target of intensive treatment was 7%-7.9%.

**Table 1.** Steps to Achieve Glucose Goals

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<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
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<tr>
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<td>Initiating treatment</td>
<td>Selecting initial drug therapy</td>
<td>Achieving glycemic control</td>
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enables insulin secretion, downregulates glucagon, and does not cause hypoglycemia.14 In addition, insulin is always an option for initial therapy and, in fact, its administration must be started if the patient is catabolic.13

Physicians are concerned about weight gain in many cases in which a TZD is prescribed. However, data do not support this concern. Depending on the study, weight gains from 1.0 to 3.6 kg are seen with TZD-treated patients who follow diet and exercise plans.15,16 The value of diet and exercise cannot be overemphasized. A patient will gain weight if using a TZD while not implementing any changes in lifestyle. If a sulfonylurea is used, an extended-release form of glipizide or glimepiride should be selected because such agents are associated with less risk of hypoglycemia.17

Step 2 is to advance oral therapy for patients with diabetes mellitus. If a patient has not achieved adequate glycemic control on a monotherapy regimen after 3 months, a second oral medication is usually added.12 Any combination of oral agents is acceptable, provided that each drug is from a different class. To enhance patient adherence, tablets containing two agents—such as metformin and sitagliptin, or metformin and a sulfonylurea or TZD—are useful. One might also consider adding exenatide to the monotherapy program if the patient is not already using a DPP-IV inhibitor. Again, insulin is a treatment option for patients at any HbA1c level.13

Step 3 involves deciding whether to use a third oral agent, introduce exenatide, or begin insulin therapy.12 If a patient fails to respond to dual oral therapy, advancing the treatment regimen in one of these directions requires patient involvement in the decision process. A guiding concept regarding how to proceed at this stage is the following: In general, each oral agent alone can reduce the HbA1c level by 1.0% to 2.0%, but each added oral agent results in further HbA1c reductions of approximately 1%.18 Exenatide will also usually reduce a patient’s HbA1c level by about 1%.19

Thus, in clinical practice, the physician usually adds exenatide or an additional oral agent to the existing regimen if the patient’s HbA1c level is 1% or less above goal. However, if the patient’s HbA1c level is more than 1% above goal, the patient is probably a candidate for insulin therapy. When insulin administration is started, many physicians stop or decrease the use of sulfonylureas.18 If the patient has been taking metformin or a TZD or both, most physicians would likely continue using these agents because they are considered “insulin sensitizers.”18 Currently, exenatide and sitagliptin are not approved by the US Food and Drug Administration for use with insulin, so their use would have to be discontinued in such cases.

Step 4 involves initiating, titrating, and advancing insulin therapy. The challenge with starting insulin therapy is to introduce it in a timely manner—not delaying it until end-organ disease develops in the patient. Insulin should be started within 3 to 6 months if combination therapy cannot achieve HbA1c goals.12,13 Regular insulin and neutral protamine Hagedorn (NPH) are effective insulin preparations, but the newer basal and prandial insulin analogs are increasingly replacing the older insulin preparations. Both regular insulin and NPH exhibit considerable intrapatient and interpatient variability in absorption.20-22

Furthermore, the long duration of action of the older insulin preparations dictated that patients had to adjust their daily dosing schedules around multiples of 4 and 8 hours to avoid hyperglycemia and hypoglycemic episodes. By contrast, the new fast-acting insulin analogs—insulin aspart, insulin glulisine, and insulin lispro—are preferred over regular insulin because they can be used at the start of a meal, are rapidly absorbed, and have short durations of action.22,23 The basal insulins—insulin glargine and insulin detemir—are preferred over NPH because they result in less nocturnal hypoglycemia.24,25

A very conservative starting point is to prescribe about 10 units of insulin—or 0.10 to 0.25 units of insulin per kilogram of body weight—on a once-daily regimen.26 These starting doses are appropriate for insulin glargine, insulin detemir, NPH, premixed 70/30 insulin aspart protamine/insulin aspart, or 75/25 insulin lispro protamine/insulin lispro. Administration of insulin glargine or insulin detemir may be started with a once-daily morning injection, while administration of NPH is often started at bedtime. Administration of premixed insulin may be started before breakfast, before dinner, or both.27,28

Oral antidiabetes agents may be used as previously discussed. Also as previously noted, use of exenatide should be discontinued when use of insulin is initiated because study results are not yet available regarding its concurrent use with insulin.

**Titration and Advancement of an Insulin Regimen**

Figure 3 shows options for advancing once-daily and twice-daily insulin regi-
mimetics, and modern insulin analogs. The second comment pertains to whether tight glycemic control is appropriate for everyone with T2DM. Ideally, every patient should be at goal for HbA1c. In reality, however, tight glycemic control requires that patients actively participate in the management of their disease, and tight management is best reserved for those patients who want to be so involved. Thus, the job of physicians is to lead patients to adopt such a proactive perspective, to educate patients on the importance of taking control of their own healthcare, to provide opportunities for patients to learn the cornerstones of effective therapy, and to make the most appropriate medical recommendations for patients.

References


