Diabetes and Cardiovascular Disease

Intensive Glucose Lowering and Cardiovascular Disease Prevention in Diabetes
Reconciling the Recent Clinical Trial Data

Theodore Mazzone, MD

Cardiovascular disease (CVD) is a very common, if not the most common, cause of morbidity and mortality in developed countries, and there has been longstanding recognition that diabetes is a potent risk factor for CVD. Individuals with either type 1 or type 2 diabetes mellitus manifest CVD rates up to 4 to 10 times higher than those observed in nondiabetic subjects. Subjects with diabetes also have been shown to have more advanced atherosclerosis, as measured by carotid intima-media thickness (CIMT) measures or coronary artery calcium (CAC) scores.

The potential pathophysiology of accelerated atherosclerosis and CVD risk in diabetes is complex (Table 1). Patients with type 2 diabetes mellitus commonly have hypertension and manifest a number of abnormalities in systemic lipid protein metabolism and in inflammatory and coagulation pathways that are predicted to be proatherogenic and to increase CVD risk on the basis of observational and mechanistic studies conducted in diabetic and nondiabetic experimental models. These abnormalities are related to coexisting insulin resistance in the majority of patients with diabetes and manifest as low-high-density lipoprotein cholesterol, increased triglyceride-rich lipoprotein cholesterol, postprandial lipemia, elevated levels of C-reactive protein and other inflammatory markers, and increased levels of plasminogen activator inhibitor 1 and fibrinogen levels. Insulin resistance in patients with type 2 diabetes mellitus is generally but not always related to obesity and may be more specifically linked to central obesity and accumulation of fat in the visceral fat depot.

In patients with type 1 diabetes mellitus, understanding of the potential pathophysiologies for accelerated atherosclerosis and CVD is complicated by the young age (usually before the second or third decade of life) of these patients at the time of diagnosis of diabetes. Because of this young age at diagnosis, many years usually pass between the diagnosis of diabetes and the appearance of clinical CVD in patients with type 1 diabetes mellitus. In addition, at the time of diabetes diagnosis, these patients typically manifest none of the proatherogenic changes associated with insulin resistance noted in type 2 diabetes mellitus. Some have suggested that CVD risk in longstanding type 1 diabetes mellitus may be related to weight gain (particularly in the central fat compartment) that may result from many years of sustained peripheral hyperinsulinemia. This accumulation of fat in the central compartment may then produce changes more typical of insulin resistance and the proatherogenic milieu common in type 2 diabetes mellitus. Alternatively, others have argued that higher rates of CVD in subjects with many years of type 1 diabetes mellitus, especially in older studies, really reflect the adverse effects of diabetic microangiopathy, specifically diabetic nephropathy (either proteinuria or azotemia), on CVD risk.

Although the underlying pathophysiology for accelerated atherosclerosis and CVD may not be completely clear, a great deal of information has become available for favorable modification of CVD risk in diabetes over the past 2 decades. Strict control of blood pressure and treatment with statin-type drugs importantly contribute to CVD risk reduction in patients with diabetes, specifically type 2, and these have become standard-of-care approaches for managing CVD risk in such patients. Even with blood pressure control and statin treatment, however, residual incremental CVD risk in diabetes remains; in many randomized controlled trials of blood pressure and statin therapy, actively treated subjects with diabetes continue to manifest higher event rates than actively treated subjects without diabetes.

In line with this, an examination of trends for CVD in diabetes shows a decline over time, but the rate of CVD events remains higher than in nondiabetes. Addressing this residual incremental risk for CVD risk in diabetes is an important problem not only from the point of view of the individual patient but also from the public health perspective, because rates of diabetes are rising dramatically in both developed and developing countries. These increasing rates are likely related to aging of the population in developed countries, improved nutrition in developing countries, and increasing rates of obesity in both. In addition to this overall increase in the incidence of diabetes, there has been a shift in the age of diagnosis of type 2 diabetes mellitus to younger patients. These patients will therefore have many more years of diabetes, with resultant increased vulnerability to clinical CVD at a younger age. In view of this ongoing epidemic of diabetes, finding ap-
approaches to preventing or delaying its CVD complications remains an important area for investigation.

The complex pathophysiologies for accelerated atherosclerosis and CVD noted above provide many potential high-value therapeutic targets for preventing or delaying CVD in diabetes. On the basis of pathophysiological considerations, targeting increased inflammation, procoagulation, or disordered lipoprotein metabolism (beyond statin therapy) are all attractive approaches.8,16,17 Hyperglycemia, of course, defines diabetes, and assessing the effect of glycemic control in preventing or delaying CVD events in diabetes has been considered important for many decades. It has been known for some time that baseline glycemia (measured as a fasting blood sugar or glycohemoglobin) predicts future CVD events and that this association can extend even into the nondiabetic glycemic range.18,19 Randomized clinical trials, both large and small, have been performed to evaluate the relationship of glycemic control to CVD in diabetes. These trials have used diverse approaches to improve glycemic control and have assessed both hard and surrogate CVD end points. Several large-scale, well-designed, well-executed trials examining the effect of glycemic control on CVD end points in both type 1 and type 2 diabetes mellitus have been completed in recent years. These trials will be examined in more detail in the next section.

Recent Randomized Clinical Trials to Evaluate the Effect of Glycemic Control on CVD Event Rates in Subjects With Diabetes

A number of large trials have been conducted recently to evaluate the impact of glycemic control on CVD events in diabetes (Table 220–24). The Diabetes Control and Complications Trial (DCCT) randomized 1441 subjects with type 1 diabetes mellitus to intensified or routine blood sugar control with insulin.25 At the time of enrollment, the patients were between 13 and 40 years of age, free of clinical CVD, and without hypertension or hypercholesterolemia. The average follow-up in this trial was 6.5 years. At the completion of the DCCT in 1994, 1394 subjects agreed to join the Epidemiology of Diabetes Intervention and Complications (EDIC) Study.20 As part of a prespecified analysis plan, follow-up data on CVD end points analyzed by original DCCT treatment-assignment group were reported in 2005.

At baseline, the subjects in the conventional-therapy group had marginally higher systolic blood pressure (115 mm Hg compared with 113 mm Hg), but no other differences were noted between the conventional-treatment and intensive-insulin-therapy group in other cardiovascular risk factors, including lipid levels, cigarette smoking, or duration of diabetes. At the end of the DCCT and the active intervention period, the conventional-treatment group had significantly higher hemoglobin A1c (9.1% versus 7.4%) and higher prevalence rates for microalbuminuria and albuminuria. The conventional-treatment group also manifested a higher prev-

Table 1. Potential Contributors to Accelerated Atherosclerosis and CVD in Diabetes

<table>
<thead>
<tr>
<th>Type 1 diabetes mellitus</th>
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<tbody>
<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Nephropathy</td>
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<tr>
<td>Late-onset central obesity and insulin resistance</td>
<td></td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased TGRL-C</td>
<td></td>
<td></td>
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<tr>
<td>Postprandial lipemia</td>
<td></td>
<td></td>
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<tr>
<td>Proinflammatory state*</td>
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<tr>
<td>Procoagulant state*</td>
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</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; TGRL-C, triglyceride-rich lipoproteins.
*Related to insulin resistance.

Table 2. CVD End-Point Trials of Intensive Glucose Control in Diabetes

<table>
<thead>
<tr>
<th></th>
<th>DCCT/EDIC20</th>
<th>UKPDS21</th>
<th>ACCORD22</th>
<th>ADVANCE23</th>
<th>VADT24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>1394 T1DM</td>
<td>3867 T2DM</td>
<td>10 251 T2DM</td>
<td>11 140 T2DM</td>
<td>1791 T2DM</td>
</tr>
<tr>
<td>Age, y</td>
<td>27</td>
<td>53</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>17</td>
<td>5.0</td>
<td>3.4</td>
<td>4.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Targets</td>
<td>Glycohemoglobin &lt;6.05%; glucose 70–120 mg/dL premeal or &lt;180 mg/dL postmeal</td>
<td>FPG &lt;6 mmol/L vs Std</td>
<td>Glycohemoglobin &lt;6% vs 7%–7.9%</td>
<td>Glycohemoglobin &lt;6.5% vs &gt;6.5%</td>
<td>Glycohemoglobin &lt;6%, 1.5% absolute reduction</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>6</td>
<td>0</td>
<td>10</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CVD, %</td>
<td>0</td>
<td>2</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Baseline BP, mm Hg</td>
<td>115/73</td>
<td>135/82</td>
<td>136/75</td>
<td>145/81</td>
<td>132/76</td>
</tr>
<tr>
<td>Baseline LDL</td>
<td>109 mg/dL</td>
<td>3.5 mmol/L</td>
<td>2.7 mmol/L</td>
<td>3.1 mmol/L</td>
<td>2.8 mmol/L</td>
</tr>
<tr>
<td>Baseline glycohemoglobin, %</td>
<td>9.1</td>
<td>7.1</td>
<td>8.3</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Result with intensive control</td>
<td>42% Reduction in CVD (P=0.02)</td>
<td>No difference</td>
<td>Increased overall mortality (HR 1.22, P=0.04)</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

T1DM indicates type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; Std, standard treatment; BP, blood pressure; and HR, hazard ratio.
alence of a creatinine level >2 mg/dL during the EDIC follow-up period.

By February 2005, with a total follow-up period of 17 years, 98 CVD events had occurred in 52 subjects in the conventional-treatment group. By comparison, there were 46 events in 31 subjects in the intensive-treatment group. There was a 57% reduction in the risk of a first occurrence of a myocardial infarction, stroke, or CVD death. These differences between the rates of CVD end points in the intensive-treatment group and the conventional-treatment group were statistically significant. In further analysis, it was noted that the difference in albuminuria and microalbuminuria contributed to the beneficial effect of intensive insulin therapy on CVD end points; however, the treatment effect remained significant even after adjustment for differences in albuminuria and microalbuminuria. The investigators of DCCT/EDIC concluded that intensive glycemic control produced a long-term benefit on CVD in patients with type 1 diabetes mellitus.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was designed to assess the impact of tight blood sugar control on CVD events in subjects with type 2 diabetes mellitus. More than 10 000 patients with a mean age of 62.2 years and a median hemoglobin A1c of 8.1% were randomly assigned to intensive glucose control (with a hemoglobin A1c goal of <6%) or standard glucose control (with a hemoglobin A1c goal of 7% to 7.9%). The median duration of diabetes in this cohort was 10 years in each group; approximately 35% of them had a previous CVD event, and there were no differences in CVD risk factors at baseline. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death due to cardiovascular causes. The trial also included arms to evaluate the impact of blood pressure and lipid interventions on CVD in type 2 diabetes mellitus. The ACCORD glycemic control arm was terminated prematurely after a mean follow-up of 3.5 years because of an excessive number of deaths in the intensive-glucose-control group. Attained glycohemoglobin levels were 6.4% and 7.5% in the intensive-treatment and standard-control groups, respectively. Two hundred fifty-seven subjects in the intensive-glucose-control group died compared with 203 in the standard-control group. Hypoglycemia that required medical assistance occurred in 10.5% in the intensive-therapy group and 3.5% in the standard-therapy group. As a result of their analysis, the ACCORD investigators concluded that intensive glucose lowering produces no benefit in terms of CVD risk reduction and even produces harm in high-risk patients with type 2 diabetes mellitus. In an analysis of prespecified subgroups in the ACCORD trial, there was a suggestion that patients who did not have a cardiovascular event before randomization and who had a baseline glycohemoglobin of 8% or less had fewer fatal or nonfatal cardiovascular events with intensive control than with standard control.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) was conducted in 11 140 patients with type 2 diabetes mellitus randomized to standard or intensive glucose control. Subjects randomized to the latter group all used gliclazide, along with other drugs as required, to achieve a hemoglobin A1c goal of 6.5% or less. The age was 66 years in each group, with a duration of diabetes of 7.9 to 8 years. Approximately 32% of subjects in each group had a history of myocardial infarction, stroke, or other major macrovascular disease. Median glycohemoglobin at baseline was 7.2% in each group. At the completion of the study (median of 5 years of follow-up), the hemoglobin A1c level was 7.3% in the standard-control group and 6.5% in the intensive-control group. The primary end points in this trial were composites of death due to cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (major macrovascular events), along with new or worsening nephropathy or retinopathy (which defined major microvascular events). The trial demonstrated that intensive control led to a significant reduction in combined major macrovascular and microvascular events (18.1% versus 20%, hazard ratio 0.90, 95% CI 0.82 to 0.98, P=0.01) and in major microvascular events (9.4% versus 10.9%, hazard ratio 0.86, 95% CI 0.77 to 0.97, P=0.01). This reduction was related primarily to a significant reduction in the incidence of nephropathy with intensive control. There was not a significant effect of intensive glucose control on major macrovascular events (hazard ratio 0.94, 95% CI 0.84 to 1.06, P=0.32), CVD death (hazard ratio 0.88, 95% CI 0.74 to 1.04, P=0.12), or all-cause mortality (hazard ratio 0.93, 95% CI 0.83 to 1.06, P=0.28). As in the ACCORD trial, severe hypoglycemia was more common in the intensive-control group; however, overall rates of hypoglycemia were much lower than in ACCORD (2.7% versus 1.5% in intensive and standard groups, respectively, hazard ratio 1.86, 95% CI 1.42 to 2.40, P<0.001). The decrease in hemoglobin A1c level in ADVANCE was considerably less rapid than that observed in ACCORD (reduction of 0.5% at 6 months and 0.6% at 12 months).

The Veterans Affairs Diabetes Trial (VADT) enrolled 1791 veterans with type 2 diabetes mellitus and randomly assigned them to intensive or standard glucose control. The primary outcome measure of this trial was time to first occurrence of a composite of myocardial infarction, stroke, cardiovascular death, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for gangrene. Mean age at time of enrollment was 60.4 years, with a mean duration of diabetes of 11.5 years. Forty percent of the enrollees had a history of a cardiovascular
event. Baseline glycohemoglobin in this trial was 9.4%, and there was no difference in cardiovascular risk factors at baseline between the 2 therapy groups. After a median follow-up of 5.6 years, glycohemoglobin levels were 6.9% in the intensive-therapy group and 8.4% in the standard-therapy group. There was no significant difference in any component of the primary outcome between the 2 groups. Rates of hypoglycemia were 24.1% in the intensive-therapy group and 17.6% in the standard-therapy group. The fall in glycohemoglobin was very rapid, as in the ACCORD trial, from 9.4% to 6.9% in the intensive-therapy group by 6 months after randomization. Although there was no significant difference in primary event rate, there was a low overall incidence of primary events in both treatment groups. The predicted event rate was 40% in the standard-therapy group, but the observed event rate was 33.5%. The predicted event rate in the intensive-therapy group was 31.6%, and the observed event rate was 29.5%. Weight gain was significantly greater in the intensive-therapy group.

The United Kingdom Prospective Diabetes Study (UKPDS) is the oldest of the large randomized glycemia control trials; it randomized subjects with type 2 diabetes mellitus to intensive blood sugar control versus standard blood sugar control. The trial enrolled patients with newly diagnosed type 2 diabetes mellitus with a median age of 54 years. The goal for intensive therapy was <6 mmol/L of fasting blood sugar. In the standard-therapy group, drugs were added if the patient experienced symptoms of hyperglycemia or fasting plasma glucose was >15 mmol/L. Hemoglobin A1c over a 10-year period was 7% in the intensive-therapy group and 7.9% in the standard-therapy group. This trial had multiple microvascular and macrovascular end points and demonstrated a significant 25% risk reduction in microvascular end points in the intensive-therapy group. This study also demonstrated a 16% risk reduction for myocardial infarction with intensive therapy, but this difference did not reach statistical significance (P=0.052). It is worth recalling that as opposed to the recently conducted large trials of glycemic control in CVD, the UKPDS trial was conducted before the widespread use of statin therapy in type 2 diabetes mellitus and in subjects with newly diagnosed diabetes and essentially no CVD.

Glycemic Control and CVD Risk in Diabetes: Why Is This Still a Question?

The previous section presents results of 5 large, well-designed, and well-executed randomized clinical trials examining the impact of tight glycemic control on CVD events in diabetes. In type 1 diabetes mellitus, there is evidence for benefit on the basis of results of the DCCT/EDIC. Four trials, including 3 reported very recently, failed to show a significant benefit of tight glycemic control on CVD rates in type 2 diabetes mellitus. In view of these consistent results in type 2 diabetes mellitus, why is the issue of glycemic control and CVD risk in type 2 diabetes mellitus still worth considering?

The 5 trials in the previous section were presented in some detail to allow a rigorously appropriate interpretation of their results. On the basis of the results of these trials, it cannot be concluded that glycemic control does not prevent CVD complications in type 2 diabetes mellitus unless this conclusion is substantially qualified. The appropriate qualifiers would include the specific pharmacotherapeutic interventions used, the patient population studied (especially with respect to age, duration of diabetes, and cardiovascular risk factors, including preexisting CVD), the baseline glycemic control, the glycemic goals, duration of the therapeutic intervention, and the period of observation. Although randomized clinical trials are justifiably the goal standard for evidence-based practice, the above trial-design characteristics (necessary to allow trial feasibility and efficiency) importantly impact the interpretation of trial results. The impact of these factors on the interpretation of trial results needs to be examined carefully when results of randomized clinical trials are not concordant with other types of evidence (for example, observational or pathophysiological evidence). In addition, and importantly, the difference between results of glycemic control in type 1 diabetes mellitus and type 2 diabetes mellitus on CVD events must be understood and rationalized. Mention has already been made of observational evidence that baseline glycemia predicts future CVD events in diabetic and nondiabetic populations. In the next sections, we will further examine other types of evidence that bear on the relationship between tight glycemic control and CVD risk in patients with diabetes.

Mechanistic and Pathophysiological Studies With In Vitro and Animal Models

Studies with isolated cells or tissue or in experimental animal models cannot unequivocally establish appropriate therapeutic approaches for human disease; however, such studies can provide plausibility and the pathophysiological context for human studies. For example, this approach has provided a detailed mechanistic underpinning for observations that relate specific native or modified lipoproteins to human atherosclerosis and clinical CVD. Over many years, a consensus has emerged in the literature relative to experimental characteristics in isolated cell studies that are consistent with proatherogenicity. Key cellular constituents in the progression from normal vessel wall to atherosclerotic plaque to vulnerable plaque to plaque rupture are thought to be endothelial cells, monocyte-derived macrophages, and arterial smooth muscle cells. In endothelial cells, the increased expression of inflammatory factors or adhesion molecules is considered proatherogenic, as are inhibitors of endothelial cell–mediated vasodilation or increased endothelial cell death. In macrophages, disturbances in sterol flux and reverse cholesterol transport that favor increased cell sterol retention, the increased expression of adhesion and inflammatory factors, or increased cell death are consistent with proatherogenicity. In arterial smooth muscle cells, factors that increase proliferation or alter the composition of the extracellular matrix are thought to be proatherogenic. The impact of hyperglycemia on the above experimental end points, in vitro and on the vessel wall in animals, has been examined (Table 3).

Studies in isolated cells have demonstrated that hyperglycemia increases adhesion of monocytes to endothelium as a...
Table 3. Hyperglycemia and the Vessel Wall

<table>
<thead>
<tr>
<th>Cell studies</th>
<th>Animal studies</th>
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<tbody>
<tr>
<td>Endothelial cells</td>
<td>Impaired vasodilation</td>
</tr>
<tr>
<td>Increased inflammatory factor expression</td>
<td>Increased aldose reductase--mediated</td>
</tr>
<tr>
<td>Increased adhesion molecule expression</td>
<td>AGE protein--mediated</td>
</tr>
<tr>
<td>Increased cell death</td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
</tr>
<tr>
<td>Increased inflammatory factor expression</td>
<td>Altered matrix production/composition</td>
</tr>
<tr>
<td>Increased adhesion molecule expression</td>
<td></td>
</tr>
<tr>
<td>Increased production of ROS</td>
<td></td>
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<tr>
<td>Dysregulation of sterol flux</td>
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<tr>
<td>Increased cell death</td>
<td></td>
</tr>
<tr>
<td>Arterial smooth muscle cells</td>
<td></td>
</tr>
<tr>
<td>Increased cell proliferation</td>
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</table>

ROS indicates reactive oxygen species.

result of increased expression of adhesion factors on both endothelial cells and monocyte-macrophages. Hyperglycemia also increases expression of nuclear factor-κB in both endothelial cells and monocyte-derived macrophages, along with increased production of superoxide and reactive oxygen species, thus producing increased oxidative stress. Increased oxidative stress can lead to increased production of oxidized low-density lipoprotein (LDL) in the vessel wall with the subsequent untoward effects experimentally ascribed to this modified lipoprotein. Hyperglycemia has been shown to impair the nitric oxide production that is important for endothelial cell--dependent vasodilation and to impair endothelial cell--dependent vasodilation in vivo. Proteins modified by advanced glycosylation end products (AGE proteins) have been shown to interrupt key steps in reverse cholesterol transport. In arterial smooth muscle cells, hyperglycemia supports proliferation and alters composition of arterial smooth muscle cell–derived matrix in a manner predicted to increase retention and subsequent oxidative modification of lipoproteins.

The relationship of hyperglycemia to the vessel wall has also been studied in animal models examining the above-described end points, as well as atherosclerosis. Many of these models, however, are confounded because the experimental interventions that produce hyperglycemia also alter lipoprotein pattern. It is uncertain, therefore, whether changes in vessel-wall cells or atherosclerosis in these models relate directly to hyperglycemia or to a more atherogenic lipoprotein profile. There are animal models, however, that do lend support to the notion that hyperglycemia is directly injurious to the vessel wall. Vikramadithyan and colleagues studied the effect of increased aldose reductase expression on atherosclerosis in the LDL-receptor–deficient, atherosclerosis-prone mouse model. Aldose reductase mediates the production of cellular toxins from glucose, and these investigators reported that in streptozotocin diabetic mice, but not nondiabetic mice, increased expression of human aldose reductase leads to more atherosclerosis. Vessel-wall cells express receptors that recognize AGE proteins, and signaling via these receptors activates a program of proinflammatory gene expression. Several laboratories have reported that modifying signaling via the receptor for AGE proteins either by reducing receptor expression, blocking binding of AGE protein to the receptor, or reducing formation of advanced glycosylation end products can reduce atherosclerosis in diabetic mouse models.

Glycemic Control and Surrogate CVD End Points in Diabetes

Measurement of CIMT by ultrasound, of CAC by computed tomography, or of coronary atherosclerosis by coronary intravascular ultrasound have been identified as providing useful markers for assessing cardiovascular risk and predicting cardiovascular events. These measurements can provide incremental information beyond that provided by routine cardiovascular risk factor assessment for predicting cardiovascular events in subjects with diabetes. Patients with type 1 and type 2 diabetes mellitus have been shown to have increased CIMT, CAC, and coronary atherosclerosis by intravascular ultrasound, and progression of these measures has been shown to be more rapid in diabetic subjects than in nondiabetic subjects. Some but not all studies have shown that progression of CIMT and of CAC scores is tightly related to measures of glycemic control even after adjustment for routine atherosclerosis risk factors.

In DCCT/EDIC, intensive insulin therapy in type 1 diabetes mellitus led to lower CAC burden and decreased progression of CIMT compared with standard insulin therapy. In subjects with type 1 diabetes mellitus, pancreas transplantation has been shown to reduce CIMT independent of changes in lipid, blood pressure, smoking, or use of hyperlipidemic drugs. In type 2 diabetes mellitus, therapeutic lifestyle changes, metformin, insulin secretagogues, and thiazolidinediones have all been shown to reduce progression of CIMT. In single trials, reduced progression cannot be clearly related to changes in glycemia; however, an analysis of a large number of trials showed that reductions in rates of progression were closely related to changes in on-treatment measures of glycemia.

Meta-Analysis, Subgroup Analysis, and Extended Follow-Up of Randomized Controlled Trials

Three separate meta-analyses have recently examined the relationship between glycemic control and CVD events in subjects with type 2 diabetes mellitus (Table 4). The first of these analyses included UKPDS, ADVANCE, VADT, ACCORD, and PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events). The latter trial randomized subjects with type 2 diabetes mellitus and macrovascular disease to placebo or pioglitazone. The participants in this trial were 62 years of age and had established CVD. Hemoglobin A1c at the time of randomization was 7.9%, and...
the average time of observation was 35.4 months. The trial randomized 5238 patients. Hemoglobin A1c fell 0.8% in the pioglitazone group and 0.3% in the placebo group from baseline to final visit. The primary end point of this trial, which was a composite of hard cardiovascular events and cardiovascular procedures, was not statistically different; however, a secondary end point that focused primarily on hard cardiovascular events showed a significant reduction. Including this trial, the 5 trials in this meta-analysis included 1497 nonfatal myocardial infarctions, 2318 coronary heart disease events, 1127 strokes, and 2892 all-cause deaths during approximately 163,000 person-years of follow-up. The glycohemoglobin concentration was 0.9% lower for the intensive-therapy group than for the standard-therapy group. There was an overall significant 17% reduction in nonfatal myocardial infarction and a 15% reduction in coronary heart disease events. There was no significant difference with regard to stroke or all-cause mortality.

The second meta-analysis included UKPDS, ACCORD, ADVANCE, and VADT. The inclusion of these trials provided information on 27,802 adult subjects and demonstrated that intensive control of glycemia significantly reduced nonfatal myocardial infarction but did not reduce risk of cardiovascular death or all-cause mortality. Subjects in the intensive-therapy group were also at increased risk for severe hypoglycemia. The third meta-analysis also included the ACCORD, ADVANCE, VADT, and UKPDS trials. Results of this analysis showed that subjects randomized for more intensive glucose control had a reduced risk of major cardiovascular events by 9% (hazard ratio 0.91, 95% CI 0.84 to 0.99) compared with those randomized to less intensive glucose control. This advantage was primarily the result of a 15% reduction in risk of myocardial infarction. As in previous meta-analyses, there was no difference in overall mortality, and subjects in the more intensive-control groups had more major hypoglycemic events. An exploratory subgroup analysis suggested that subjects without preexisting macrovascular disease may have benefited from intensive glycemic control more than subjects with preexisting disease. Therefore, the results of all 3 meta-analyses demonstrated a benefit of improved glycemic control on nonfatal myocardial infarction but no difference in overall mortality. Authors of the meta-analyses pointed out the limitations of this approach, including the use of summary rather than individual data in the analyses by Ray et al and Kelly et al.

The large group sizes incorporated into the design of the recently reported trials of glycemic control on CVD risk in type 2 diabetes mellitus lend themselves to a number of prespecified subgroup analyses. One of the most provocative of these was conducted in subjects with varying levels of coronary artery atherosclerosis (as quantified by CAC) in the VADT (Table 4). Analysis of a subgroup of 301 study participants with a mean follow-up duration of 5.2 years indicated that subjects with lower baseline CAC benefited more from intensive glycemic control than those with higher scores. For those subjects with CAC >100, the multivariable hazard ratio for an end point event was 0.74 (95% CI 0.46 to 1.20, P=0.21) for those randomized to intensive treatment, whereas it was 0.08 (95% CI 0.008 to 0.77, P=0.03) for those randomized to intensive therapy with a CAC ≤100.

The results of the UKPDS trial were presented in a previous section and also were included in each of the meta-analyses described above. As noted previously, there was a 16% reduction in myocardial infarction in UKPDS that did not reach statistical significance at the time the trial was ended and reported in 1998. At the time of trial completion, the majority of patients (78%) continued to be followed up, but without differences in therapeutic intervention. Seven aggregate clinical outcomes were prespecified for analysis on an intention-to-treat basis according to the previous UKPDS randomization group. The differences in glycohemoglobin between the intensive-therapy and routine-therapy groups were lost 1 year after trial completion in 1998, and glycohemoglobin remained essentially identical in the 2 previously defined treatment groups over the course of a 10-year follow-up. After an additional 10 years of follow-up, the investigators reported a 15% reduction in myocardial infarction in the group previously randomized to intensive therapy. This is similar to the percent reduction reported immediately after completion of the trial, but with the occurrence of additional events, this reduction became significant (P=0.01). Subjects originally randomized to the intensive-therapy group also demonstrated 13% less overall mortality (P=0.007) after the additional 10 years of follow-up.

Table 4. Hyperglycemia and CVD in Type 2 Diabetes Mellitus: Meta-Analyses, Extended Follow-Up, and Subgroup Analyses

<table>
<thead>
<tr>
<th>Meta-analyses</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ray et al</td>
<td>33,21 UKPDS 34,36 ACCORD, ADVANCE, VADT,24 PROactive57</td>
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<tr>
<td>Kelly et al</td>
<td>27,802 Subjects Reduced CVD events (10%) No change in cardiovascular or all-cause mortality Increased hypoglycemia</td>
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<tr>
<td>Turnbull et al</td>
<td>27,049 Subjects Reduced MI (15%) No change in cardiovascular or all-cause mortality Increased hypoglycemia</td>
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<tr>
<td>Holman et al</td>
<td>3277 Subjects Reduced CVD events (15%) Reduced all-cause mortality (13%) Total follow-up 17–18 y Glycohemoglobin 8.1% at start of extended 10-y follow-up</td>
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<tr>
<td>Low-CAC subgroup (VADT)</td>
<td>301 Subjects Reduced CVD events (HR 0.08)</td>
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MI indicates myocardial infarction; HR, hazard ratio.
Managing CVD Risk in Diabetes: Glycemic Control in Context

DCCT/EDIC demonstrated that intensive glycemic control in type 1 diabetes mellitus produces benefit for preventing CVD events. This result, along with observational and pathophysiological data, establishes control of glycemia as an integral aspect of the management of long-term CVD risk in subjects with type 1 diabetes mellitus. This issue, however, is somewhat more complex for type 2 diabetes mellitus. Several large randomized clinical trials failed to show a benefit of intensive glycemic control on overall CVD, and without such data, it is impossible to establish an unequivocal recommendation for glycemic control as a means of managing CVD risk in subjects with type 2 diabetes mellitus. There are, however, important considerations that suggest glycemic control can be part of managing CVD risk in this patient population. First, the data discussed above in type 1 diabetes mellitus from DCCT/EDIC provide a reasonable proof-of-concept that hyperglycemia is toxic to the vessel wall in humans. Furthermore, studies in isolated cells and in animals provide several plausible mechanisms for this toxicity. Measures of atherosclerosis in humans by CIMT or CAC are also consistent with vessel-wall injury from hyperglycemia and reduced atherosclerosis with better glycemic control. Meta-analysis of the major end-point trials demonstrates a CVD benefit for intensive glycemic control in type 2 diabetes mellitus, and a 10-year extended follow-up of 1 of the clinical trials (UKPDS) provided evidence of benefit that approximated the benefit predicted by the meta-analyses. This extended follow-up also demonstrated a benefit of intensive glycemic control on overall mortality. Finally, an important subgroup analysis in VADT demonstrated that subjects with less coronary artery disease (as evaluated by amount of CAC) derived a significant benefit from intensive glycemic control with respect to prevention of CVD events.

Several reasonable scenarios could be considered for the inconsistency of individual randomized clinical trial results with other types of data mentioned above. The relationship between glycemic control and CVD could be complicated by an adverse effect of glucose variability on vessel-wall homeostasis. Furthermore, although hyperglycemia may be toxic to the vessel wall, it may be of overall less importance relative to other factors present in type 2 diabetes mellitus, for example, dyslipidemia, hypertension, inflammation, and procoagulation. There are a great deal of pathophysiological data and observational data suggesting that inflammation and coagulation contribute substantially to CVD risk in subjects with type 2 diabetes mellitus; however, there are as yet very few interventional data. In fact, it could be argued that the data supporting a benefit for managing hyperglycemia are superior to those addressing inflammation or coagulation for primary prevention of CVD in type 2 diabetes mellitus. On the other hand, randomized clinical trial data to date suggest that statin treatment and hypertension management will have a more profound effect on reducing the CVD event rate in type 2 diabetes mellitus than hyperglycemia management. The CVD benefits of statin therapy or one of multiple approaches to managing hypertension in type 2 diabetes mellitus have been demonstrated clearly in terms of reduction of overall events and reduction of CVD mortality within a 5-year period of intervention/observation in multiple trials.

The 2 largest randomized clinical trials evaluating the impact of statin therapy on CVD events in subjects with diabetes are the Collaborative Atorvastatin Diabetes Study (CARDS) and the Heart Protection Study (HPS). In CARDS, 2838 subjects with type 2 diabetes mellitus, 40 to 75 years of age and with no previous history of CVD, were randomized to atorvastatin 10 mg/d or placebo. At baseline, subjects had a glycohemoglobin of 7.8%. At trial entry, LDL cholesterol level was less than 4.14 mmol/L, and fasting triglyceride was less than 6.78 mmol/L. The primary end point of the trial was the first occurrence of acute coronary heart disease events, coronary revascularization, or stroke. Subjects had a mean follow-up of 3.9 years, and the trial was terminated 2 years early. At the time of trial termination, there was a significant (P=0.001) 30% reduction in primary end point events in the atorvastatin group. Subjects who entered the trial with LDL cholesterol levels above and below 3.1 mmol/L benefited similarly from atorvastatin treatment. In addition, there was no influence of baseline glycohemoglobin on benefit. Rates of death were also reduced in the atorvastatin group by 27%, but this did not reach statistical significance at 3.9 years (P=0.059).

In HPS, 5963 subjects with diabetes (both type 1 and type 2) who were 40 to 80 years old, with or without preexisting vascular disease, were randomized to simvastatin 40 mg/d or placebo. The primary end point of the trial included hard major vascular events. The mean duration of follow-up was 4.8 years; baseline LDL cholesterol in this trial was 3.2 mmol/L, and baseline fasting triglyceride was 2 to 2.3 mmol/L. Treatment with simvastatin produced a 22% reduction in primary end point events (P<0.0001). Subjects with baseline LDL cholesterol above and below 3.5 mmol/L or glycohemoglobin above or below 7% benefited similarly from simvastatin treatment.

Although the best data for the benefit of aggressive treatment of dyslipidemia in diabetes belong to the statin class of antilipemic drugs, multiple classes of antihypertensive drugs have been shown to produce cardiovascular benefit in subjects with diabetes. Reviews of a large number of end-point trials that included use of thiazide diuretics, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and β-blockers have supported a systolic blood pressure goal of 130 to 135 mm Hg and a diastolic blood pressure goal of 80 mm Hg in diabetes. Overall, analyses fail to support the superiority of any one class of drug, and reduction of hard CVD end points generally ranged from 20% to 30% with 3 to 5 years of follow-up. The overall greater importance of aggressive lipid and blood pressure control compared with glycemic control is also supported by analysis of results of the Steno-2 trial. In this trial, a multifactorial approach to management of CVD risk in type 2 diabetes mellitus (including lipid, blood pressure, and glucose control) reduced CVD death by >50% at 13.3 years of follow-up. Subsequent analysis of these results suggested statins and antihypertensive treatment provided the largest benefit, with glucose control next.
Other reasons why well-designed and well-executed randomized clinical trials could fail to demonstrate a benefit relate to the patient population studied, types of intervention, period of intervention, and period of observation. For example, a subgroup analysis has already suggested that starting therapy in patients with less established coronary atherosclerosis may be beneficial. A long-term follow-up of UKPDS has suggested that a longer period of observation after institution of glycemic control may be necessary to observe a CVD benefit. It is also possible that the drugs currently available for achieving intensive blood sugar control produce untoward effects that counterbalance any CVD benefit provided by such control. The most obvious of these untoward effects would be hypoglycemia, which is much more common in patients with intensive glycemic control targets. Analysis of the ACCORD data could not establish a relationship between hypoglycemia and increased mortality in the intensive-control group. A meta-regression analysis, however, did suggest a link between hypoglycemia and cardiovascular mortality. Serious hypoglycemic reactions can be nocturnal, frequently go unnoticed, and can produce long-term activation of the sympathetic nervous system. In elderly patients with coronary artery disease or other similarly vulnerable patients, this physiological response to hypoglycemia could elevate the risk of myocardial infarction, cardiac arrhythmia, or death.

In view of all the available data, managing glycemia as an aspect of managing overall CVD risk in subjects with both type 1 and type 2 diabetes mellitus remains a viable proposition. In addition to all of the considerations above, it is important to recall that intensive glycemic control has been shown to produce a substantial benefit for preventing long-term microvascular complications in both type 1 and type 2 diabetes mellitus. Although CVD is the major cause of death in subjects with diabetes, microvascular complications produce substantial morbidity. Furthermore, prevention of microvascular complications, specifically nephropathy, could also produce a long-term benefit for prevention of CVD (Figure). Several professional organizations have made recommendations for glycemic targets after consideration of recent data from large randomized clinical trials. In general, a glycohemoglobin goal of 7% is believed appropriate; however, it is emphasized that goals need to be individualized for patients. For example, more intensive goals could be appropriate for a young patient with no CVD, whereas less intensive goals are appropriate for the elderly or for those with established CVD in whom the risk associated with hypoglycemia could be significant. In support of this approach, a recent observational study concluded that better glycemic control is associated with better cardiovascular outcomes in diabetic subjects with fewer comorbidities. Recent evidence suggests that the prevalence of diabetes in the United States will approximately double in the next 2 to 3 decades. Although additional randomized clinical trial data examining the relationship of glycemic control to CVD could certainly be of value, the size and duration of such a trial given what we now know (for example, the need to study lower-risk patients over a longer period of time) could make its cost prohibitive. Clinicians caring for patients with diabetes need to make decisions about optimal management of

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**Figure.** Hyperglycemia could promote atherosclerosis and CVD events by altering hepatic and peripheral lipoprotein metabolism, by facilitating development of proteinuria and azotemia, or by modulating oxidative stress, inflammation, and macrophage-endothelial cell adhesion in the vessel wall.
CVD risk. Currently available evidence makes it reasonable to include glycemic control, with a target individualized to the patient, as part of an overall risk-management strategy in this rapidly increasing population of patients.

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References


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Theodore Mazzone

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