Many of the microvascular and macrovascular complications of type 2 diabetes mellitus (T2DM) are already present when the diagnosis is first made. About 20% of patients diagnosed as having diabetes have microvascular complications such as retinopathy, erectile dysfunction, or nephropathy. Approximately 50% already have evidence of atherosclerotic vascular disease. One-third of patients who have a myocardial infarction (MI) or undergo coronary artery bypass grafting (CABG) are diagnosed with diabetes at the time of their event. Patients diagnosed as having diabetes who have concurrent cardiovascular disease (CVD) have a poorer prognosis than those who do not have CVD.

Diabetes is the leading cause of microvascular diseases that lead to end-stage renal disease, dialysis, and adult diabetic blindness. Diabetic peripheral neuropathy, present in 60% to 70% of people with diabetes, can result in nontraumatic amputations. Macrovascular disease complications from diabetes, such as CVD, MI, and stroke, lead to a 2- to 4-fold increased risk of death. The mortality risk for men with diabetes is substantially higher than that of men without diabetes; for women, the mortality risk is even greater. Every increase in glycated hemoglobin (HbA1c) can increase the cardiovascular event rate by up to 18% and the microvascular event rate by up to 30%.

Three strategies are needed to lower the cardiovascular risk of people with diabetes:

- aggressive control of blood pressure
- control of diabetic dyslipidemia: low-density lipoprotein cholesterol (LDL-C) should be less than 100 mg/dL for primary prevention and less than 70 mg/dL for secondary prevention
- stabilization of glucose values

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Recent clinical trials have investigated whether intensive glucose-lowering therapy for people with T2DM will reduce their risk of microvascular and macrovascular events. These trials (United Kingdom Prospective Diabetes Study [UKPDS], Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease [ADVANCE], Veterans Affairs Diabetes Trial [VADT]) provided evidence that aggressive glycemic control reduces risk of microvascular complications.

The Diabetes Control and Complications Trial (DCCT) demonstrated benefits in patients with type 1 diabetes mellitus. However, the observation that aggressive glycemic control reduces macrovascular complications was not readily apparent.

**DCCT**

The DCCT, which began in 1983, was a landmark study that investigated intensive glucose control in patients with type 1 diabetes mellitus. The 1440 enrolled patients were divided into 2 groups: (1) those treated aggressively with 4 insulin injections daily or insulin pump therapy, and (2) those treated with routine care that included less monitoring and fewer injections daily. Researchers reported a 50% to 60% reduction in microvascular complications among patients treated more aggressively. There was also a 40% reduction in cardiovascular events; however, this reduction was not statistically significant. This finding could be due to the fact that the study included only people with type 1 diabetes mellitus and examined a younger population, which has a lower likelihood of developing complications.

**UKPDS**

The UKPDS7 followed 5100 patients with T2DM for 10 years and investigated whether intensive control of glucose would decrease complications. This study7 also examined whether any of the currently available oral treatments for diabetes were superior. Patients were treated with metformin, sulfonylureas, insulin, or lifestyle changes. The effects of intensive blood pressure control on complications were also assessed. The fasting plasma glucose goal was less than 108 mg/dL, and the blood pressure goal was less than 150/90 mm Hg.

The trial found a significant reduction in combined diabetes-related endpoints, powered primarily by a 25% reduction in microvascular endpoints and by 16% reduction (not statistically significant) in myocardial infarction (Figure 1) with intensive glucose control.7 This decrease came from a reduction of HbA1c levels of only 1% (7.9% vs 7.0%).7

Further analysis of the relationship between glycemia and risk reduction indicated that each 1% reduction in updated mean HbA1c was associated with reductions in risk of 21% for any endpoint related to diabetes (95% confidence interval, 17%-24%; P<.0001), 21% for deaths related to diabetes (15%-27%, P<.0001), 14% for myocardial infarction (8%-21%, P<.0001), and 37% for microvascular complications (33%-41%, P<.0001).11 No threshold for HbA1c was observed for risk reduction of any endpoint.11 This observation led to the speculation that if patients with diabetes had even more aggressive glycemic goals, microvascular and macrovascular complications could be further reduced. Instead of setting HbA1c goals of 7% to 8%, patients with diabetes could potentially aim for normal HbA1c levels.

Findings from the UKPDS also indicated that patients treated with metformin had a reduction in diabetes-related endpoints, all-cause mortality, and myocardial infarction.12 Although the number of obese patients who were treated with metformin was relatively small, the results indicated that metformin may be beneficial for reduction in cardiovascular events.

Data from these studies7,11,12 as well as similar data from the smaller Kumamoto study,13 showed that intensive glucose control in both type 1 and type 2 diabetes mellitus reduced microvascular complications, but more data were needed to answer the question about whether tight glycemic control would significantly reduce cardiovascular events (Table).

Three major trials—ACCORD, ADVANCE, VADT—have focused on the effect of intensive glucose control on cardiovascular events in patients with T2DM.

**ACCORD**

The ACCORD trial14 was a randomized trial that included more than 10,000 high-risk patients with T2DM.

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Figure 1. Impact of intensive blood-glucose control on complications in patients with a glycated hemoglobin level of 7.9% vs 7.0%. Source: United Kingdom Prospective Diabetes Study Group. Lancet. 1998;352(9131):837-853.
Interestingly, there seemed to be a positive trend in reduction of all cardiovascular events, except cardiovascular death, among patients in the intensive treatment arm.\textsuperscript{16}

The posthoc analyses suggested that people who had T2DM for less than 12 years received benefit from intensive control.\textsuperscript{17} In contrast, those with a longer duration of diabetes had no benefit or were adversely affected.\textsuperscript{18} Further, the increased mortality was best explained by those patients that received the intervention but still were unable to reach the goal. These results underscore the importance of aggressively treating diabetes as early as possible, preferably at the time of diagnosis.

### Table

**Lowering HbA1c Levels Reduces Complications in Patients With Type 1 and Type 2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Complications</th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9.1%</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63%</td>
<td>69%</td>
<td>17%-21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24%-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>41%*</td>
<td></td>
<td>16%*</td>
</tr>
</tbody>
</table>

* Not statistically significant.

**Abbreviations:** DCCT, Diabetes Control and Complications Trial; HbA1c, glycated hemoglobin; NA, not applicable; UKPDS, United Kingdom Prospective Diabetes Study.


There were three treatment arms, and each arm was matched to a control or standard therapy group, as follows:

- Intensive glucose control: treatment, HbA1c less than 6%; control, 7% to 9%
- Intensive blood pressure management: treatment, systolic blood pressure less than 120 mm Hg; control, diastolic blood pressure less than 80 mm Hg
- Statin therapy use: treatment, fibrate plus statin therapy; control, statin alone\textsuperscript{14}

Participating physicians were able to choose the medication used for glucose control. At the time, thiazolidinediones (TZDs) and insulin were used frequently as treatments in the United States.

The average HbA1c level at the start of the trial was 8.1%. The final HbA1c was 6.4% in the intensive treatment group and 7.5% in the standard treatment group when that arm of the trial was terminated at 3.5 years because of excessive deaths in the intensive treatment group.\textsuperscript{14} This study\textsuperscript{14} provided the first evidence of the possibility that intensive glucose control could harm patients. Interestingly, there seemed to be a positive trend in the composite primary outcome when the trial was stopped, mostly due to a decrease in nonfatal MIs.

The negative results from the ACCORD trial have a number of explanations. Explanations for higher mortality in this study include higher baseline HbA1c levels, longer duration of diabetes, increased rates of severe hypoglycemia, and advanced CVD at enrollment of the study.\textsuperscript{14} Thus, participants already had an increased risk of mortality.

**ADVANCE**

Based in Australia, the ADVANCE trial\textsuperscript{15} was an international trial that included more than 11,000 high-risk patients with T2DM. Investigators examined whether intensive glucose control would provide any additional benefit compared with standard care.

At the conclusion of the trial, there was a significant reduction in the composite of microvascular and macrovascular events; however, the benefit was almost entirely derived from a decrease in microalbuminuria and nephropathy.\textsuperscript{15} When only cardiovascular events were considered, there was no significant benefit of intensive glucose lowering.

**VADT**

The VADT\textsuperscript{16} evaluated the efficacy of intensive glucose control on major cardiovascular events, including heart failure and limb ischemia requiring amputation, in patients who were no longer responsive to oral agents. The trial enrolled 2000 veterans with T2DM who were treated with intensive glucose control or standard therapy.\textsuperscript{16}

Intensive glucose control, defined as HbA1c levels less than 7%, did not significantly reduce major cardiovascular events; however, there were significantly fewer cardiovascular events in both groups than predicted. There was a favorable trend in reduction of all cardiovascular events, except cardiovascular death, among patients in the intensive treatment arm.\textsuperscript{16}

The Legacy Effect

The Epidemiology of Diabetes Interventions and Complications (EDIC) trial was the epidemiologic follow-up of the participants in the DCCT trial, which was previously described. After the intervention period, participants received care as directed by their physician. After a 10-year follow-up, the HbA1c levels were nearly identical among those intensively treated for 6 years compared to those who had received the standard therapy (7.1% vs 7.2%, respectively). However, for the intensively treated participants, a 42% reduction in cardiovascular endpoints and a 57% reduction in myocardial infarction was observed.\textsuperscript{19} These findings were the first evidence that intensive glucose control, even for a temporary period, could have an effect on cardiovascular events later in life. This effect is referred to as the legacy effect.

Similar results were observed with epidemiologic follow-up data from the UKPDS. When patients were followed for 10 years after interventions were terminated, the HbA1c level differences in the treatment group and the control group had disappeared at 10 years.\textsuperscript{18} Despite similar HbA1c levels in the two treatment groups, those patients who had received intensive glucose control had a significant reduction in any diabetes endpoint, a significant reduction in MI, and an overall reduction in death. Those patients treated with metformin had an even greater reduction in MI and death from any cause.\textsuperscript{18}

These follow-up studies\textsuperscript{18,19} strongly suggest that intense glycemic control...
could improve cardiovascular outcomes in diabetic patients years later; however, more clinical trials are required to further characterize this legacy effect.

**Lipid and Blood Pressure Control**

Diabetes is not simply a disease of glucose control; it is an interaction between lipids, blood pressure, and glucose. Thus, major clinical trials have also studied the effects of lipid and blood pressure control in diabetic patients. The ADVANCE\(^{15}\) and VADT\(^{16}\) studies showed similar lipid and blood pressure control. In the UKPDS\(^{7}\) blood pressure was controlled at 150/90 mm Hg, which is no longer considered intensive blood pressure control. The benefit of tight blood pressure control in that trial exceeded the benefit of glucose control, indicating that even mediocre blood pressure control was more effective than glucose control.

Data from the Steno-2 trial on combined control of glucose, lipids, and blood pressure levels demonstrated significant short- and long-term benefits from this combined approach.\(^{20}\) The effect seems to be more cumulative than synergistic. However, recent results from ACCORD indicate that intensive lipid control (addition of a fibrate to statin therapy) or intensive blood pressure does not reduce cardiovascular events.\(^{21,22}\)

In summary, ACCORD, ADVANCE, and VADT indicate that aggressive glucose control will benefit microvascular complications, but more data are needed to understand the optimum time and treatments to provide cardiovascular benefit. There is some evidence suggesting that intense glucose control may be beneficial in patients with a shorter duration of diabetes, indicating that diabetes needs to be aggressively treated as early as possible to reduce the risk of macrovascular complications.\(^{23}\) The follow-up UKPDS\(^{28}\) and DCCT\(^{19}\) suggest that the effect of intensive glucose control on cardiovascular outcomes may not be apparent until years later, creating a legacy effect or metabolic memory, even if the intensive glucose control is temporary. Physicians may therefore need to carefully consider which of their patients would actually benefit from aggressive glycemic control.

### Risks of Tight Glycemic Control

Despite the benefits of reductions in cardiovascular risks, the data also indicate that tight glycemic control can increase other risks, such as hypoglycemia and weight gain. Moreover, intensive treatment requires a greater number of medications with additional expense for the patient and healthcare system and offers the potential for drug interactions between agents.

As stated previously, the ACCORD trial was terminated prematurely because of increased deaths and cardiovascular events. There was also a significant increase in severe hypoglycemia in the ACCORD trial, and it was initially speculated that the increase contributed to the study’s negative results. The risk of hypoglycemia was also apparent in the UKPDS trial. For example, an overall increase in severe episodes as well as total episodes of hypoglycemia was observed in patients treated with sulfonylureas, metformin, and insulin.\(^{31}\) The risk of severe hypoglycemia increases as HbA\(_1c\) approaches normal levels. This increase forces clinicians to consider the safety of such low HbA\(_1c\) levels in diabetic patients, and what the optimal risk-benefit ratio of HbA\(_1c\) levels should be.

Weight gain is also associated with tight glycemic control. There are various negative metabolic effects associated with weight gain, which lead to a greater burden of treatment. The risk of weight gain is apparent in the ACCORD trial, where a substantially greater number of intensively treated patients gained more than 10 kg in the routine care arm. In the UKPDS, there was significantly higher weight gain in the insulin and sulfonylurea treatment arms compared to the conventional treatment arm.\(^{11}\)

All of the diabetes treatments available when these studies began, with the exception of metformin, had negative effects on weight (Figure 2). Sulfonylureas, glinides, thiazolidinediones, and insulin typically lead to weight gain.\(^{24}\) Metformin, incretin mimetics, dipeptidyl peptidase-4 inhibitors, and pramlintide are typically weight-neutral or may even lead to weight loss.\(^{24}\)

According to the treatment algorithm put forth jointly by the American Diabetes Association and the European Association for the Study of Diabetes, metformin is recommended as first-line therapy.\(^{25}\) However, the progressive nature of the disease will require the use of combination therapy in many patients over time.\(^{25}\) If metformin is combined with other agents, weight gain is more likely. Patients with T2DM who need to lose weight are often frustrated when the treatment for diabetes contributes to weight gain. When choosing additional treatments for diabetes, the physician must take into consideration the treatment’s effects on weight and how much of a concern weight gain would be for each individual patient.

There are a variety of reasons that a diabetic medication could lead to weight gain. People typically gain weight when they improve their glycemic control as they stop the glucosuria seen in hyperglycemia and allow deposition of glucose to glycogen stores. The physician should remind the patient that this weight gain will not continue. Furthermore, patients who fear hypoglycemia may begin eating defensively to prevent lows before they happen. Moreover, a patient can rebound from hypoglycemia caused by overeating. Lastly, certain treatments result in weight gain or increased appetite as a result of fluid retention.

Metformin has been associated with lactic acidosis. Thus, creatinine clearance of patients who are taking this medication should be monitored. For a young person, a creatinine clearance of 1.4 to 1.5 mg/dL is acceptable. If the glomerular filtration rate is below 50 mL per minute on two tests, metformin treatment should be terminated. If the patient is in a nursing home, risk of weight loss is a significant consideration with metformin administration. Because patients in nursing homes need to maintain their weight to maintain their immunity, metformin may not be the ideal therapy. In fact, some physicians have begun to recommend abstaining from the use of metformin in elderly patients.

### Management of Type 2 Diabetes

When choosing a treatment for diabetes, physicians should consider glucose targets. For example, if a patient has primarily fasting hyperglycemia, a treat-
Regimen is helpful. When testing for diabetes, patients can use meters to record pre- and postprandial blood glucose levels. For a patient with T2DM who is taking an oral therapy such as metformin, checking blood glucose levels twice a week is sufficient as long as the tests occur at different times of the day to account for diurnal variability.

Figure 2. Weight changes in patients with type 2 diabetes mellitus by therapy based on a retrospective review conducted from 1996 to 2002. A total of 9546 patients started and were kept on stable therapy for at least 12 months. Predictors of weight gain were younger age, male gender, higher glycated hemoglobin level, and use of a selective serotonin reuptake inhibitor. Abbreviations: MET, metformin; SU, sulfonylurea; T2D, thiazolidinedione. Source: Nichols GA et al. Presented at 65th Annual Session of American Diabetes Association; San Diego, CA; June 2005.

For example, one week could test fasting blood glucose levels, the next week could test blood glucose levels after lunch, and the following week could check levels after dinner. If a patient is on an agent that can cause hypoglycemia (such as a sulfonylurea), then more frequent glucose monitoring may be necessary. If the patient is already on insulin therapy, the patient should check blood glucose before every injection.

All told, the average patient with T2DM will usually need seven distinct medications to manage their blood pressure, glucose, and lipids. This medication amount poses a clinically significant burden in terms of medication adherence, side effects, and drug interactions. As a result, several factors, from efficacy to side effects to ease of use, should be considered before choosing a therapy for patients taking several medications. Figure 3 presents 11 recommended questions physicians should ask as they consider diabetes medications for their patients.

Conclusion

Clinical trials have shown that tight glycemic control reduces microvascular complications, but the current data from these large randomized trials indicate that it does not initially reduce cardiovascular events. Follow-up analyses for these trials have found a possible legacy effect, suggesting that a positive cardiovascular benefit occurs in later years. If the correct treatment strategies for individual patients are implemented appropriately and if patients are treated more aggressively at diagnosis, the cardiovascular complications of diabetes may be reduced.

References


