Prevention of Cardiovascular Disease in Persons with Type 2 Diabetes Mellitus: Current Knowledge and Rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

David C. Goff, Jr., MD, PhD,a,b,* Hertzel C. Gerstein, MSc, MD,c Henry N. Ginsberg, MD,d William C. Cushman, MD,e Karen L. Margolis, MPH, MD,f Robert P. Byington, MPH, PhD,a John B. Buse, MD, PhD,g Saul G bench, MD,h Jeffrey L. Probstfield, MD,i and Denise G. Simons-Morton, MD, PhD,j for the ACCORD Study Group†

Patients with type 2 diabetes mellitus die of cardiovascular disease (CVD) at rates 2–4 times higher than patients without diabetes but with similar demographic characteristics. The prevalence of diabetes is increasing in the United States and, thus, the prevention of CVD in patients with diabetes poses an urgent public health challenge. The objective of this report is to review the current knowledge base for the prevention of CVD in patients with diabetes, with particular emphasis on the control of glycemia, lipids, and blood pressure. Epidemiologic analyses suggest that each 1% increase in glycosylated hemoglobin increases the risk for CVD by approximately 18%; however, evidence from the randomized trials that have examined whether glucose lowering reduces this risk is conflicting. Randomized trials have shown that lowering low-density lipoprotein cholesterol reduces CVD event rates by 17%–43% in patients with diabetes. Limited data support a role for lowering triglycerides and increasing high-density lipoprotein cholesterol in the prevention of CVD. Evidence from clinical trials shows that reducing systolic blood pressure to \(<140 \text{ mm Hg}\) results in 30%–60% reductions in CVD events; however, epidemiologic evidence suggests that lowering to optimal systolic blood pressure levels \(<120 \text{ mm Hg}\) may be additionally beneficial. Important questions regarding prevention of CVD in patients with diabetes remain unresolved, including the benefits of near-normal glycemic control, comprehensive therapy for diabetes-related dyslipidemia, and optimal blood pressure control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial will test hypotheses to address these unanswered questions. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:4i–20i)

Type 2 diabetes mellitus is a complex disease characterized by hyperglycemia, insulin resistance, and variable degrees of insulin deficiency. Patients with type 2 diabetes have a high rate of cardiovascular disease (CVD) mortality, non-fatal myocardial infarction (MI), and stroke. This CVD risk is related in part to a high prevalence of other CVD risk factors, such as elevated blood pressure and dyslipidemia. Indeed, the combination of diabetes with hypertension and/or dyslipidemia confers a much greater CVD risk than either risk factor alone. Moreover, as in people without diabetes, there is a graded increase in risk with higher blood pressure and total serum cholesterol levels.

As the prevalence of diabetes increases in the United States, the associated CVD prevalence is also expected to

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*Address for reprints: David C. Goff, Jr, MD, PhD, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA. E-mail address: dgoff@wfubmc.edu.

† A complete list of the members of the ACCORD Study Group is included in the Appendix.

*Departments of Epidemiology and Prevention and bInternal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; cDepartment of Medicine and the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; dDepartment of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA; eMemphis Veterans Affairs Medical Center, Memphis, Tennessee, USA; fBerman Center for Outcomes & Clinical Research, Hennepin County Medical Center, Minneapolis, Minnesota, USA; gDivision of General Medicine and Clinical Epidemiology, Department of Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA; hDepartment of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; iDivision of Cardiology, Department of Medicine, University of Washington Medical Center, Seattle, Washington, USA; and Clinical Applications and Prevention Branch, Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA.

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increase. Because of the urgency of this public health challenge, the analyses of recent clinical trials have focused on the effects of control of glycemia and other CVD risk factors on complication rates in patients with diabetes. Most of those trials, however, either included few patients with diabetes or were not designed to address CVD prevention. More importantly, in lipid and hypertension trials that did show that reducing cholesterol and blood pressure lowered the risk for CVD events in patients with diabetes, the absolute rates remained very high despite these interventions.

The clinical trials completed to date highlight the current gap in knowledge regarding the relative CVD benefits of targeting normal glucose, blood pressure, and lipid levels. As a result, since 1997, scientists on 3 different panels organized by the National Institutes of Health (NIH) have concluded that a major randomized clinical trial was needed to determine the effects of intensive glycemic control, as well as lipid and/or blood pressure control, on CVD in patients with type 2 diabetes. Such a trial was funded beginning in 1999 and is scheduled to end participant follow-up in 2009. The purpose of this report is to review what is currently known about the prevention of CVD in patients with diabetes by controlling glycemia, lipids, and blood pressure. Important unanswered questions that will be addressed by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial are identified in each of these areas. This report also includes a brief discussion regarding other aspects of a comprehensive strategy to prevent CVD in patients with diabetes and closes with a brief description of the hypotheses and main features of the ACCORD trial.

Methods

Pertinent references were identified using Medline database searches of reports related to the prevention of CVD in patients with diabetes. Searches focused on the identification of reports published from January 1990 through January 2003. In addition, more recent reports from major studies and the reference lists of selected reports were reviewed. Pertinent results from randomized controlled trials were synthesized qualitatively.

Diabetes and the risk for CVD: Diabetes is a strong independent risk factor for CVD.1 Compared with their counterparts without diabetes, the relative risk for CVD is 2–3 times greater in men with diabetes and 3–4 times greater in women with diabetes.2–8 This risk is independent of the risk associated with other classic risk factors, such as hypercholesterolemia, smoking, and hypertension.2 Population-based studies report that approximately 45% of white adults with diabetes have coronary artery disease (CAD), compared with 25% in individuals without diabetes,9 and that middle-aged patients with diabetes have an annual risk for fatal and nonfatal CVD of 2%–5%.2,10–13 Data collected in the recent Heart Outcomes Prevention Evaluation (HOPE) study14 reflected these high risks and showed that they applied even in 1999, despite the use of therapies proved to reduce CVD risk. In that large multicenter trial, 1,769 high-risk patients with diabetes who were randomized to placebo experienced a 4.5-year rate of MI, stroke, or cardiovascular death of 19.8% (4.4% per year), despite baseline treatment rates of 56% for aspirin, 20% for diuretics, 29% for β-blockers, and 22% for lipid-lowering agents. In addition, patients with diabetes may not be experiencing as great a decrease in CAD mortality as persons without diabetes15; however, more recent studies examining CVD incidence and hospitalization rates have not replicated these findings.16,17

Patients with diabetes also have poor prognoses after CVD events. Prospective studies have reported that the relative risk for mortality after an MI is 2–3 times greater in patients with diabetes than in individuals without diabetes.8,18,19 This higher risk also applies to patients with diabetes and unstable angina. In a recent analysis of data from the international Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry of hospitalized patients with unstable angina (21% with diabetes), the absolute rates for MI, stroke, or CVD mortality within 2 years of admission were 16.9% and 9.7% for patients with and without diabetes, respectively.20

The results of the Steno-2 Study (Steno Diabetes Center, Copenhagen, Denmark) provide broad support for the contention that CVD risk can be reduced in patients with type 2 diabetes.21 In this trial, 160 patients with type 2 diabetes and microalbuminuria were randomized to an intensive multifactorial intervention targeting glycemia, blood pressure, dyslipidemia, and microalbuminuria or to conventional care. The risk for a cardiovascular event was reduced by 53% (95% confidence interval [CI], 27%–76%) over 8 years of follow-up. The relative roles of the various interventions and whether these results will apply more broadly to patients without microalbuminuria are not known. In aggregate, these observations provide strong support for the need for additional research focused on specific treatments for the primary and secondary prevention of CVD in patients with diabetes.

Glucose as a target for the prevention of CVD in patients with type 2 diabetes: Large, prospective epidemiologic studies in patients with diabetes have shown that higher glucose levels predict higher rates of CVD22–31 and that the risk for a CVD event is greater at higher values of glycosylated hemoglobin (HbA1c) (Table 1).32,33 A recent meta–regression analysis of epidemiologic studies reported that the risk for a CVD event was 18% greater for each 1% increase in HbA1c.34 Other recent epidemiologic research has shown that this CVD–glucose relation extends below glucose thresholds used to define diabetes into the normal fasting and postprandial ranges.35–43 These observations provide strong support, though certainly not proof, for the
hypothesis that lowering glucose to levels within the normal range might prevent CVD.

The possibility that blood glucose level may be a modifiable CVD risk factor is supported by a growing body of data from clinical trials (Table 2). The United Kingdom Prospective Diabetes Study (UKPDS) was the first trial to show that a policy of intensive glycemic control using oral agents or insulin can reduce clinical outcomes in patients with type 2 diabetes. In the main study of 3,867 patients with newly diagnosed type 2 diabetes, a fasting plasma glucose level <6 mmol/L (1 mg/dL = 0.05551 mmol/L) was targeted by initial therapy with either a sulfonylurea or insulin. Other agents were added when needed. Using this approach, the intensive group achieved a median HbA1c level of 7.0% (interquartile range, 6.2%–8.2%) over a 10-year period and experienced a 25% relative risk reduction (RRR) in microvascular outcomes and a 12% RRR in all diabetes-related end points compared with a policy that achieved a median HbA1c level of 7.9% during this period. There was a reduced risk for MI of borderline statistical significance, with an observed RRR of 16% (95% CI, 0%–29%; p = 0.052).

A separate randomization of 1,704 obese participants at 15 UKPDS centers allocated 342 obese participants to intensive control with metformin, 951 to intensive control with sulfonylureas or insulin, and 411 to conventional control. The median HbA1c levels were 7.4% in the intensive group.
groups treated with metformin, sulfonylureas, or insulin and 8.0% in the conventional group during the first 10 years of follow-up. Despite a modest separation in HbA1c among groups, the metformin group had a 32% risk reduction in any diabetes-related end point, a 42% risk reduction in diabetes-related death, a 36% risk reduction in all-cause mortality, and a 39% risk reduction in MI. There was a nonsignificant 29% reduction in microvascular outcomes. Of note was the observation that intensive control with metformin led to significantly lower rates of any diabetes-related end point, all-cause mortality, and stroke than intensive control with sulfonylureas or insulin.

In another randomization of obese and nonobese intensive-group participants in the UKPDS trial, metformin was added or not added to a sulfonylurea if the fasting plasma glucose level was 6.1–15 mmol/L. Contrary to the results of the main trial, in this subgroup, there was a 96% increase in diabetes-related deaths and a 60% increase in all-cause mortality in those randomized to the early addition of metformin. These conflicting metformin results leave uncertainty regarding the best drugs to treat patients with type 2 diabetes. Taken together, these UKPDS reports suggest that a policy of lowering glycemia in patients with type 2 diabetes reduces clinically important outcomes. The benefit of lowering glycemia is especially clear for microvascular disease, and there is a possibly reduced risk for CVD that requires further study.

Evidence from other trials of intensive glycemic control further supports the hypothesis that such glycemic control may reduce CVD and highlights the need for more research in this area (Table 2). The Kumamoto Study of insulin-based intensive control in 110 nonobese Japanese patients with type 2 diabetes reported a CVD event rate of 0.6 per 100 patient-years in the intensive group and 1.3 per 100 patient-years in the conventional group (ie, a nonsignificant RRR of 46%). In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study of intensive insulin-based glycemic control during the immediate postinfarct period and for the first 3 months after MI, an HbA1c level of 7.0%, compared with 7.5%, was associated with a 29% lower mortality rate at 1 year and a 25% lower mortality rate at 3.4 years. When this trial was recently replicated, no difference in mortality was reported; however, there was no contrast in HbA1c levels between the treatment groups. In the variable insulin dose arm of the University Group Diabetes Program (UGDP) study, there was also a nonsignificant trend in favor of reduced cardiovascular deaths. Most recently, in type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study reported a 50% reduction in CVD outcomes in participants treated intensively (mean, HbA1c 7.2%) during the randomized trial phase compared with participants treated conventionally (mean, HbA1c 9.1%) during that phase.

The results of other studies suggest that intensive glycemic control may worsen CVD outcomes. The 2-year feasibility phase of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes Mellitus (VA CSDM) trial found that the intensively treated group had a nonsignificant increase in the risk for CVD events. Possible explanations for this result include the short duration of the trial, the use of a sulfonylurea-class drug in the intensive group but not in the conventional group, and the relatively few events. Regardless of the reason, these results underscore the need for a definitive trial to evaluate the potential CVD benefits and risks of near-normal glycemic control.

Finally, it is important to note that intensive glycemic control poses risk. The proved risks are hypoglycemia and increased weight gain, and in randomized trials of patients with type 2 diabetes, these risks were greatest in insulin-treated patients. Table 3 lists the risks observed in major trials and suggests that 2%–3% of patients with type 2 diabetes who achieve mean HbA1c and fasting plasma glucose concentrations approaching normal with intensive insulin therapy will have ≥1 severe hypoglycemic reactions annually. In addition to the risks of glucose-lowering per se, adverse effects due to the agents used to lower glucose may also occur. These effects include the possibility that sulfonylureas may increase the risk for arrhythmias, especially in an ischemic myocardium; that metformin increases the risk for lactic acidosis and gastrointestinal symptoms; and that the available thiazolidinediones increase the risk for anemia, edema, and possibly congestive heart failure. The impact of these risks may be magnified in middle-aged and older patients with high baseline risk for cardiovascular events.

When considered as a whole, the available epidemiologic and clinical trial data support, but do not prove, the hypothesis that near-normal glycemic control reduces CVD events in patients with type 2 diabetes. They also highlight the possibility that intensive therapy is associated with significant risks. Available data support the need for a definitive randomized clinical trial to evaluate the CVD benefits and risks of tight glycemic control in patients with type 2 diabetes.

**Dyslipidemia as a target for the prevention of CVD in patients with type 2 diabetes:** The relation between lipoprotein concentrations and the risk for CVD is similar in patients with and without diabetes; however, the risk at any specific lipoprotein concentration is much greater in patients with than without diabetes. In fact, diabetes increases the risk for CVD mortality by 2-fold to 4-fold at any level of total cholesterol, which almost certainly translates to an increase in CVD risk at any level of low-density lipoprotein (LDL) cholesterol. As a result of these findings, the Adult Treatment Panel (ATP) III guideline of the National Cholesterol Education Program (NCEP) declared the presence of diabetes as a CVD equivalent and set an LDL cholesterol
The dyslipidemia of diabetes is characterized by mildly to moderately decreased high-density lipoprotein (HDL) cholesterol and increased triglyceride concentrations. Men with diabetes have LDL cholesterol concentrations that are similar to men without diabetes; women with diabetes have modest decreases in LDL cholesterol levels compared with women without diabetes. This lipid profile reflects a high secretion of apolipoprotein B100-containing very-low-density lipoprotein (VLDL) and LDL cholesterol.\(^60\)–\(^63\) It is believed that increased free fatty acid flux to the liver in insulin-resistant patients drives triglyceride synthesis and the assembly of VLDL. In patients with type 2 diabetes, hyperglycemia may contribute to increased VLDL secretion as well, although the correction of blood glucose concentrations only partly reverses the dyslipidemia.\(^64\) Patients with type 2 diabetes also have low plasma HDL cholesterol concentrations, a finding that does not seem to be related to either glycemic control or mode of treatment.\(^65\)\(^66\) Small, dense LDL particles are commonly present in patients with type 2 diabetes. This pattern is most likely an integral part of the dyslipidemia of insulin resistance.\(^67\)\(^68\)

Several primary and secondary prevention trials of cholesterol lowering have demonstrated remarkable reductions in CAD events and mortality in high-risk patients. Treatment to lower LDL cholesterol levels has resulted in consistent reductions in cardiovascular events, beginning with the landmark Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),\(^69\) in which cholestyramine was used, and continuing through the secondary prevention trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) (such as the Scandinavian Simvastatin Survival Study [4S]),\(^70\) the Cholesterol and Recurrent Events [CARE] trial,\(^71\) the Long-Term Intervention With Pravastatin in Ischaemic Disease [LIPID] trial,\(^72\) the Post Coronary Artery Bypass Graft [Post CABG] trial,\(^73\) the Lescol Intervention Prevention Study [LIPS],\(^74\) the Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE-IT] trial,\(^75\) the Treating to New Targets [TNT] trial,\(^76\) and the Prospective Study of Pravastatin in the Elderly at Risk [PROSPER])\(^77\) and the primary prevention statin trials (such as the West of Scotland Coronary Prevention Study [WOSCOPS]),\(^78\) the Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS]),\(^79\) the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT],\(^80\) and the Collaborative Atorvastatin Diabetes Study [CARDS]).\(^81\) In several of the secondary prevention studies, there were relatively small numbers of patients with type 2 diabetes who seemed to benefit as much or more than those without diabetes. The results of these trials observed in patients with diabetes have been reviewed in detail by Vijan and Hayward.\(^82\) They reported that the use of cholesterol-lowering medications for primary and secondary prevention was extremely effective at reducing major cardiovascular events. In primary prevention, treating 35 patients for approximately 4 years prevented 1 event, whereas in secondary prevention, 1 event was prevented by treating 14 patients for approximately 5 years. More recently, the Cholesterol Treatment Trialists’ Collaborators\(^83\) reported a 22% RRR for major coronary events and a 21% RRR for major vascular events for each reduction of 1 mmol/L in LDL cholesterol in patients with diabetes. One major coronary event might be prevented for every 46 patients with diabetes treated for approximately 4.7 years (the mean trial duration), and 1 major vascular event might be prevented for every 28 patients with diabetes treated.

The Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (HPS) provided evidence of reducing CVD and mortality by treating a large group of patients with diabetes with a fixed dose of simvastatin. This large trial (20,536 participants) showed a significant reduction in all-cause mortality and a marginally significant reduction in CVD mortality in the intervention group receiving simvastatin compared with placebo. Participants had coronary disease, other occlusive arterial disease, or diabetes at baseline. The proportional reduction in the event rate associated with simvastatin treatment was similar...
in each subcategory, including the group of 5,963 participants with diabetes.\textsuperscript{84} In general, the results of subgroup analyses in these studies showed very high rates of CVD events and mortality in patients with type 2 diabetes and demonstrated substantial reductions in outcomes in the treated groups, consistent with the overall results of these trials.\textsuperscript{71,72,85} The recently published, large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)\textsuperscript{86} compared treatment with open-label pravastatin to usual care in 10,355 participants, including 3,638 with diabetes. Although this trial failed to show a significant effect on either total mortality or CAD events, there was only a 9% difference in total cholesterol and a 17% difference in LDL cholesterol levels between the treatment groups because of an unanticipated high rate of lipid-lowering therapy in the usual-care group.

CARDs studied the effectiveness of a fixed (10 mg/day) dose of atorvastatin in 2,838 patients with diabetes.\textsuperscript{81} Atorvastatin treatment significantly reduced the primary end point of time to acute CAD event, coronary revascularization, or stroke. All-cause mortality was reduced by 27% (p = 0.059). In TNT, 10,003 patients with stable CAD were randomized to atorvastatin 10 or 80 mg/day.\textsuperscript{76} During the study, LDL cholesterol was 101 mg/dL in the 10-mg/day group and 77 mg/dL in the 80-mg/day group. The primary event rates during the median follow-up period of 4.9 years were 10.9% in the 10-mg/day group and 8.7% in the 80-mg/day group (p < 0.001). There was no effect of atorvastatin 80 mg/day compared with 10 mg/day on total mortality. In 1,501 patients with diabetes, primary events occurred in 17.9% of patients in the 10-mg/day group and in 13.8% of those in the 80-mg/day group (p = 0.026).\textsuperscript{87} The results of these statin trials in participants with diabetes are presented in Table 4. Overall, these results support the importance of the intensive control of LDL cholesterol in patients with type 2 diabetes.

This evidence indicates clearly that lowering LDL cholesterol is beneficial for patients with diabetes. However, the event rates in the treated subgroups of patients with diabetes were generally higher than those in the treated subgroups of patients without diabetes and were usually similar to the rates observed in the untreated (placebo) subgroups of patients without diabetes. This observation motivates the search for benefits beyond standard treatment of LDL cholesterol. Although one option is to treat to even lower levels of LDL cholesterol, another is to treat other aspects of the dyslipidemia characteristic of diabetes. Limited data support a role for lowering triglycerides and increasing HDL cholesterol for primary and secondary prevention. In the Helsinki Heart Study (HHS),\textsuperscript{88} gemfibrozil lowered LDL cholesterol modestly but also lowered triglycerides and increased HDL cholesterol, and the reduction in cardiac events in that primary prevention trial was linked by multiple regression analysis to the increase in HDL cholesterol. Although few patients with diabetes were included in that study, a trend toward benefit was seen in patients with diabetes (Table 5).\textsuperscript{88–90} The Diabetes Atherosclerosis Intervention Study (DAIS)\textsuperscript{89} compared treatment with micronized fenofibrate and placebo for the correction of lipoprotein abnormalities in 418 participants with type 2 diabetes. The results suggested that treatment with fenofibrate reduces the angiographic progression of CAD in type 2 diabetes. Additionally, the fenofibrate group showed a consistent pattern of reduction in cardiac end points, which was not statistically significant.

In the Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT),\textsuperscript{90} treatment with gemfibrozil reduced new CAD events by 22% over a 5-year period in men with CAD and diabetes and LDL cholesterol levels of about 110 mg/dL. Gemfibrozil treatment was associated with a 25% reduction in triglycerides, a 6% increase in HDL cholesterol, and no change in LDL cholesterol. Notably, participants with diabetes had high event rates in the placebo-treated and the gemfibrozil-treated groups (Table 5). In VA-HIT, the baseline LDL cholesterol level was near the current treatment target. Even so, the event rate for the patients with diabetes was almost twice as high as for patients without diabetes. Importantly, VA-HIT has suggested that increasing HDL cholesterol and lowering triglycerides can provide significant benefits, even for patients with near-target LDL cholesterol levels. The results of VA-HIT motivate the hypothesis that even after statin therapy, the addition of fibrates in patients with diabetes will further reduce event rates significantly.

In contrast to VA-HIT, the Bezafibrate Infarction Prevention (BIP) trial did not show a benefit from fibrate treatment in a secondary prevention population.\textsuperscript{91} The patient population was not the same, however, in that LDL cholesterol levels were much higher (approximately 150 vs 110 mg/dL in VA-HIT) and triglycerides lower (approximately 145 vs about 180 mg/dL [1 mg/dL = 0.01129 mmol/L] in VA-HIT). A post hoc subgroup analysis of the BIP trial showed a significant reduction in CVD end points in the group that had baseline triglyceride levels >200 mg/dL (about 15% of the patients). Approximately 10% of the patients in BIP had diabetes, but no analysis of that subgroup has been published. However, it is likely that they made up a significant portion of the patients with triglyceride levels >200 mg/dL.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study\textsuperscript{92} also did not demonstrate a reduction in coronary events, the primary end point in this trial comparing fenofibrate with placebo in 9,795 participants with diabetes. The observed 5-year rates were 5.2% and 5.9% with fenofibrate and placebo, respectively (p = 0.16). However, the rate of total CVD events, a secondary end point, was lower in participants who received fenofibrate (12.5%) than in those who received placebo (13.9%) (p = 0.035). Furthermore, a greater proportion of participants randomized to placebo (17%) than fenofibrate (8%) initiated statin therapy, and this imbalance might have masked a modestly greater treatment effect. Taken together, these results highlight residual uncertainty
Blood pressure as a target for the prevention of CVD in patients with type 2 diabetes: There is a graded increase in the risk for CVD across the entire physiologic range of blood pressure in patients with diabetes; furthermore, diabetes increases the risk for cardiovascular events 2-fold to 3-fold across the range of systolic blood pressure or diastolic blood pressure. Therefore, diabetes and high blood pressure combined confer a much greater risk for CVD than either one alone. In part because of this greater risk, observed even at high-normal levels of blood pressure, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommended beginning drug treatment in patients with diabetes with systolic blood pressure ≥130 mm Hg or diastolic blood pressure levels ≥85 mm Hg, with a blood pressure treatment goal of <130/85 mm Hg. However, at the time these recommendations were made, there were no completed clinical trials supporting the recommendations.

Table 6 describes the results of the clinical trials of blood pressure lowering in patients with diabetes. In a

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients with Diabetes (N)</th>
<th>Placebo/Control Event Rate (%)</th>
<th>Statin/Intervention Event Rate (%)</th>
<th>RRR (%)</th>
<th>Event Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>155</td>
<td>8.4</td>
<td>4.8</td>
<td>43</td>
<td>Fatal and nonfatal MI, unstable angina, sudden death</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>2,532</td>
<td>11.9</td>
<td>9.2</td>
<td>23</td>
<td>Total cardiovascular events*</td>
</tr>
<tr>
<td>CARDS</td>
<td>2,838</td>
<td>2.5</td>
<td>1.5</td>
<td>37</td>
<td>Fatal CAD, nonfatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularization, and stroke</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>202</td>
<td>45</td>
<td>22</td>
<td>51</td>
<td>Fatal CAD and nonfatal MI</td>
</tr>
<tr>
<td>CARE</td>
<td>602</td>
<td>37</td>
<td>29</td>
<td>22</td>
<td>Fatal CAD, nonfatal MI, and revascularizations</td>
</tr>
<tr>
<td>LIPID</td>
<td>782</td>
<td>23</td>
<td>19</td>
<td>17</td>
<td>Fatal CAD and nonfatal MI</td>
</tr>
<tr>
<td>Post CABG</td>
<td>116</td>
<td>26</td>
<td>15</td>
<td>47</td>
<td>Cardiovascular death, nonfatal MI, nonfatal stroke, PCI, CABG</td>
</tr>
<tr>
<td>LIPS</td>
<td>202</td>
<td>38</td>
<td>22</td>
<td>47</td>
<td>Cardiovascular death, nonfatal MI, PCI, CABG</td>
</tr>
<tr>
<td>PROVE-IT–TIMI 22</td>
<td>734</td>
<td>35</td>
<td>29</td>
<td>17</td>
<td>Death from any cause and major cardiovascular event†</td>
</tr>
<tr>
<td>TNT</td>
<td>1,501</td>
<td>18</td>
<td>14</td>
<td>25</td>
<td>Fatal CAD, nonfatal MI, resuscitated cardiac arrest, or fatal or nonfatal stroke</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>5,963</td>
<td>25</td>
<td>20</td>
<td>20</td>
<td>Fatal CAD, nonfatal MI, fatal and nonfatal stroke, coronary and noncoronary revascularization</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>3,638</td>
<td>NR</td>
<td>NR</td>
<td>11</td>
<td>Fatal CAD and nonfatal MI</td>
</tr>
<tr>
<td>PROSPER</td>
<td>623</td>
<td>18</td>
<td>23</td>
<td>-27§</td>
<td>Fatal CAD, nonfatal MI, fatal and nonfatal stroke</td>
</tr>
</tbody>
</table>

* The primary outcome in ASCOT-LLA included cardiovascular death, nonfatal MI, unstable angina, chronic stable angina, nonfatal stroke, peripheral arterial disease, retinal vascular thrombosis, revascularization procedures, transient ischemic attacks, and reversible ischemic neurologic deficits.
† PROVE-IT compared pravastatin 40 mg/day as the control group with atorvastatin 80 mg/day as the intervention group. Major cardiovascular events included MI, unstable angina hospitalizations, PCI, CABG, and stroke.
§ PROSPER reported a nonsignificant 27% increase in risk associated with the use of pravastatin in patients with diabetes.

regarding the potential CVD benefits of controlling diabetes-related dyslipidemia other than LDL cholesterol levels and the importance of testing whether such comprehensive dyslipidemia control prevents CVD events.

The comprehensive management of diabetes-related dyslipidemia might be based on the use of fibrates in combination with statins. The risk for myositis and rhabdomyolysis was clearly increased by this combination when gemfibrozil was the fibrate used. However, recent studies suggest that there is no increased risk for myositis when fenofibrate is used in combination with a statin.
post hoc subgroup analysis of participants with type 2 diabetes in the Systolic Hypertension in the Elderly Program (SHEP).\textsuperscript{97} major CVD events were reduced by 34%. Although the RRR was similar in participants with and without diabetes, the absolute risk reduction was twice as great in participants with diabetes as in those without. In the Systolic Hypertension in Europe (Syst-Eur) trial,\textsuperscript{98} patients with diabetes were reported in a post hoc subgroup analysis to have significant reductions in CVD mortality, all CVD events, and stroke. In a post hoc analysis of participants with diabetes in the Hypertension Optimal Treatment (HOT) study,\textsuperscript{99} major CVD events were reduced by 51% (p = 0.005) in those randomized to a diastolic blood pressure goal of ≤80 mm Hg compared with a goal of ≥90 mm Hg. However, the number of events was relatively small. The blood pressure achieved for the more intensively treated participants with diabetes was 144/81 mm Hg, compared with 148/85 mm Hg in the group with the goal of ≥90 mm Hg, for a blood pressure difference of 4/4 mm Hg,\textsuperscript{102} and no difference in CVD event rates was observed between randomized groups in the entire HOT population. Therefore, the HOT results do
not address the potential CVD benefits and risks of controlling systolic blood pressure to levels <130 mm Hg.

In the UKPDS, patients with hypertension and type 2 diabetes were randomized to more intensive or less intensive blood pressure control (a goal of <150/85 vs <180/105 mm Hg). Average blood pressure over 9 years was 144/82 and 154/87 mm Hg in the groups with more intensive and less intensive blood pressure control, respectively. Diabetes-related end points were reduced by 24% (p = 0.005), deaths related to diabetes by 32% (p = 0.019), strokes by 44% (p = 0.013), and microvascular end points by 37% (p = 0.009). Although not statistically significant, all-cause mortality was lower by 18% and MI by 21%. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial, a prospective, randomized, blinded trial in patients with hypertension and diabetes, compared the effects of moderate control of blood pressure (target diastolic blood pressure 80–89 mm Hg) with those of intensive control of blood pressure (target diastolic blood pressure 75 mm Hg) on the incidence and progression of diabetes-related nephropathy, retinopathy, CVD, and neuropathy. The mean blood pressure achieved in the intensive-control group was 132/78 mm Hg, compared with 138/86 mm Hg in the moderate-control group. There were no differences in any microvascular end points for the 2 blood pressure goals. The intensive-therapy group had a lower mortality rate of 5.5% compared with 10.7% (p = 0.037), but there were no statistically significant differences in MI, cerebrovascular events, or heart failure to account for the mortality difference.

In a recent meta-analysis, the Blood Pressure Trialists’ Collaboration reported that total major cardiovascular events were reduced to a comparable relative extent in patients with and without diabetes by regimens based on angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, angiotensin receptor blockers, and diuretics or β-blockers. There was limited evidence that lower blood pressure goals produced larger reductions in relative risk for total major cardiovascular events in patients with diabetes than without diabetes. This latter finding provides support for conducting a more definitive test of the ACCORD blood pressure–lowering hypothesis.

The HOT study and UKPDS provide the most definitive clinical trial evidence to date and support a blood pressure goal of <150/85 mm Hg (UKPDS) and a diastolic blood pressure goal of <80 mm Hg (HOT) in patients with hypertension and diabetes. These goals and the achieved blood pressure levels in other trials are consistent with a systolic blood pressure goal of 140 mm Hg in patients with diabetes. No trials, including ABCD, have confirmed CVD benefits of treating to lower blood pressure goals. In particular, no trial has tested whether reduction to “optimal” levels, as defined in JNC VI (ie, systolic blood pressure <120 mm Hg), would provide additional CVD benefits.

Other aspects of a comprehensive approach to the prevention of CVD in patients with diabetes: Substantial evidence supports the importance of diet and physical activity in the cause and prevention of CVD, acting in large part through influences on blood pressure, lipids, and inflammation. Furthermore, medical nutrition therapy, physical activity, and weight control are considered essential components of successful glycemic control. Hence, advice and education on nutrition (eg, macronutrient, sodium, and alcohol intake), physical activity, and weight loss should be provided to all patients with diabetes. There are consistent results from cross-sectional and prospective studies showing enhanced risk for microvascular and macrovascular disease, as well as premature mortality, from the combination of smoking and diabetes. Although there is minimal information on the effectiveness of smoking cessation specifically in patients with diabetes, there is no reason to assume that cessation would be less effective in this population.

Large-scale collaborative trials and meta-analyses of trials support the view that low-dose aspirin lowers the rate of recurrent cardiovascular events in men and women with diabetes and CVD. Substantial evidence suggests that low-dose aspirin therapy should also be used as a primary prevention strategy in men and women with diabetes who are at high risk for cardiovascular events. On the basis of these studies, the American Diabetes Association (ADA) also recommends low-dose aspirin as secondary prevention and as primary prevention in high-risk men and women age >30 years with diabetes. At present, uncertainty exists regarding whether other antiplatelet therapies (eg, aspirin plus dipyridamole or clopidogrel) may be superior to aspirin in patients with diabetes.

Evidence supports the effectiveness of ACE inhibition in reducing adverse outcomes in patients with type 2 diabetes. The HOPE study compared the ACE inhibitor ramipril with placebo in participants at high risk for CVD and found a 25% reduction in the combined outcome of MI, stroke, and cardiovascular death, which did not appear to be entirely explained by the small degree of blood pressure reduction with ACE inhibitor therapy. The effect was significant in participants with and without diabetes, participants with and without histories of CAD, and participants with and without microalbuminuria. In the subgroup of patients with diabetes, there was a reduction in relative risk in patients with and without microalbuminuria and in patients with and without hypertension, although the effects in some of the subgroups did not reach statistical significance. There is considerable evidence that ACE inhibitors improve renal outcomes (nephropathy and albumin excretion) in patients with type 2 diabetes compared with placebo in participants with hypertension as well as participants without hypertension with or without microalbuminuria. On the basis of this evidence, ACE inhibitors can be recommended for reducing cardiovascular morbidity and mor-
Unanswered questions regarding the prevention of CVD in patients with diabetes: Despite recent advances in knowledge, the prevention of CVD remains a major challenge for patients with diabetes. Several important questions regarding prevention of CVD in diabetes remain unanswered, including the benefits of intensive, near-normal glycemic control; comprehensive therapy for diabetes-related dyslipidemia; and optimal blood pressure control. The ACCORD trial will test hypotheses derived from these unanswered questions.

Details regarding the overall design of the trial are presented elsewhere in this supplement.117 However, Table 7 lists several main features of the trial. The overall goal of the ACCORD trial is to determine whether CVD event rates can be reduced in patients with diabetes by intensively targeting 3 important CVD risk factors: hyperglycemia, dyslipidemia, and high blood pressure. Specifically, the trial is testing the effects of intensive glycemic control, of treatment to increase HDL cholesterol and lower triglycerides (in the context of good LDL cholesterol and glycemic control), and of intensive blood pressure control (in the context of good glycemic control) on major CVD events in 10,251 participants, using a randomized, multicenter, double 2 × 2 factorial design. All participants were randomly allocated to target either near-normal glycemia or more standard glycemic goals. Participants randomized to the intensive group have an HbA1c target of <6.0%. Patients randomized to the standard group have an HbA1c target of 7.0%–7.9%, with an expectation that the median HbA1c level will be approximately 7.5%. Treatment regimens were designed to reach these goals using currently available antihyperglycemic drug classes and behavioral interventions in the 2 groups. In addition, 5,518 of the participants with dyslipidemia were also randomly allocated to fenofibrate or placebo (in the presence of simvastatin therapy, up to 40 mg/day, for good LDL cholesterol control). The other 4,733 participants had evidence of high blood pressure and were randomly allocated to target 1 of 2 systolic blood pressure goals (in the context of protocol-defined glycemic control): <140 or <120 mm Hg. Most currently available antihypertensive drug classes are available for use in the 2 groups. All participants receive nutrition and physical activity counseling and recommendations regarding the use of antiplatelet agents and ACE inhibitors. Current smokers receive smoking cessation counseling.

The primary outcome measure for the trial is the first occurrence of a major cardiovascular event, specifically nonfatal MI, nonfatal stroke, or cardiovascular death.117 A vanguard phase with 1,174 participants recruited from January through June 2001 was conducted to evaluate the feasibility of achieving specified protocol goals. The remaining participants were recruited from February 2003 to October 2005. Ultimately, 10,251 participants were randomized. Participants will be followed for 4–8 years (approximate mean, 5.6 years). Secondary outcomes include an expanded macrovascular outcome (the primary end point plus any revascularization plus hospitalization for heart failure), total mortality, cardiovascular mortality, major CAD events, total stroke, congestive heart failure death, health-related quality of life, cost-effectiveness, the progression of retinopathy, and a composite microvascular end point (renal failure, retinal photocoagulation, or vitrectomy). By addressing several important and currently unanswered questions regarding the prevention of CVD in patients with type 2 diabetes, the results of the ACCORD trial should influence the care of patients with type 2 diabetes for many years to come.

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Appendix