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

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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 mm Hg results in 30%–60% reductions in CVD events; however, epidemiologic evidence suggests that lowering to optimal systolic blood pressure levels (<120 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. **(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, nonfatal 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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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) study[14] 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 diabetes[15]; 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 CVD[22–31] and that the risk for a CVD event is greater at higher values of glycosylated hemoglobin (HbA_{1c}) (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 HbA_{1c}.[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

Table 1
Relation between glycemia and risk for cardiovascular (CV) disease in type 2 diabetes mellitus

Study	N	Mean Age (yr)	F/U (yr)	Glycemia*	Outcome	Rate (%)	RR	RR/1% HbA_{1c} Increase
Andersson et al[24]	411	66	7.4	SMBG ≥7.8 vs <7.8 mmol/L	Death	44 vs 32	1.4	NA
Kuusisto et al[23]	229	68	3.5	HbA_{1c} ≥7% vs <7%	CAD death	12 vs 3	4.3	NA
				HbA_{1c} ≥7% vs <7%	All CAD	20 vs 13	1.6	NA
Gall et al[25]	328	56	5.3	HbA_{1c} ≥7.8% vs <7.8%	CV death	10.4 vs 4.6	2.2	1.3
Agewall et al[26]	94	67	6.3	NA	CV death	NA	NA	1.54
Lehto et al[32]	1,059	58	7.2	HbA_{1c} ≥10.7% vs <10.7%	CAD death	NA	1.4	NA
Wei et al[28]	4,875	52	7.5	FPG 8–11.5 vs <8 mmol/L	CV death	6.3 vs 2.8	2.9	NA
Turner[27]	3,055	52	7.9	HbA_{1c} >7.5% vs <6.2%	Fatal MI	NA	1.72	NA
					MI/angina	NA	1.52	1.11
Moss et al[22]	1,780	66.6	8.3	NA	IHD death	NA	NA	1.1
					Stroke death	NA	NA	1.17
Fu et al[30]	479	61.2	4	HbA_{1c} >8.4% vs <6.3%	ECG MI/angina	30.8 vs 20.3	1.5	1.17

CAD = coronary artery disease; ECG = electrocardiographic; FPG = fasting plasma glucose; F/U = follow-up; HbA_{1c} = glycosylated hemoglobin; IHD = ischemic heart disease; MI = myocardial infarction; NA = not available; RR = relative risk; SMBG = self-monitored blood glucose.

* For SMBG and FPG, 1 mg/dL = 0.0551 mmol/L.

Adapted with permission from *Evidence-Based Diabetes Care.*[33]

Table 2
Glucose-lowering trials and cardiovascular disease (CVD) in patients with diabetes mellitus

Study	Follow-Up (yr)	Mean HbA_{1c} (%)		FPG (mmol/L)*		Therapy	Outcome	RRR for CVD (%)
		Intensive	Control	Intensive	Control			
UKPDS[44]	10	7.0	7.9	—	—	Insulin/SU	MI	16
UKPDS[45]	10.7	7.4	8.0	—	—	Metformin	MI	39
Kumamoto Study[46]	6	7.1	9.4	—	—	Insulin	CV events	46
VA CSDM[47]	2.3	7.1	9.3	—	—	Insulin/SU	CV events	−56†
DIGAMI[48]	1	7.1	7.9	—	—	Insulin	Mortality	29
DIGAMI[49]	2.1	~6.5	~6.5	—	—	Insulin	Mortality	−19
UGDP (IVAR)[50]	12.5	—	—	7.2–8.1	9.4–10.3	Insulin	CV deaths	9
Type 1 diabetes[51]‡	2–7	7.6	8.7	—	—	Insulin	Any event	45
Type 1 diabetes[51]‡	2–7	7.6	8.7	—	—	Insulin	First event	28

CV = cardiovascular; DIGAMI = Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction trial; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; IVAR = variable insulin group; MI = myocardial infarction; NS = not significant in the report and no confidence interval reported; RRR = relative risk reduction; SU = sulfonylurea; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; VA CSDM = Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes Mellitus.

* For FPG, 1 mg/dL = 0.0551 mmol/L.

† Calculated from crude data in the report.

‡ From a meta-analysis of all studies of tight control in type 1 diabetes.

Adapted with permission from *Evidence-Based Diabetes Care.*[33]

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[33]).[44–51] 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 HbA_{1c} 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 HbA_{1c} level of 7.9% during this period.[44] 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.[45] The median HbA_{1c} levels were 7.4% in the intensive

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 HbA_{1c} 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%).[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 HbA_{1c} level of 7.0%, compared with 7.5%, was associated with a 29% lower mortality rate at 1 year[48] and a 25% lower mortality rate at 3.4 years.[52] When this trial was recently replicated, no difference in mortality was reported; however, there was no contrast in HbA_{1c} levels between the treatment groups.[49] 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.[50] 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, HbA_{1c} 7.2%) during the randomized trial phase compared with participants treated conventionally (mean, HbA_{1c} 9.1%) during that phase.[53]

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.[47] 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[54] lists the risks observed in major trials and suggests that 2%–3% of patients with type 2 diabetes who achieve mean HbA_{1c} and fasting plasma glucose concentrations approaching normal with intensive insulin therapy will have $\geq$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[55]; 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.[56] 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.[2] As a result of these findings, the Adult Treatment Panel (ATP) III guideline of the National Cholesterol Education Program (NCEP)[57] declared the presence of diabetes as a CVD equivalent and set an LDL cholesterol

Table 3
Risks of intensive treatment with insulin in patients with type 2 diabetes mellitus

Study	HbA_{1c} (%)	FPG (mmol/L [mg/dL])	Hypoglycemia		Mean Weight Gain
			Severe*	Any	
UKPDS[44]	7.1	—	1.8%/yr	28%/yr	4 kg more than in control group over 10 yr
Kumamoto Study[46]	7.1	—	0%	1.9%/yr	BMI increased from 20.5 to 21.2 over 6 yr
VA CSDM[47]	7.3	—	3%/yr	41%/yr	Same as control
DIGAMI[48]	7.0	—	—	—	1 kg/yr
UGDP (IVAR)[50]	—	6.7 (120.6)	3.2%	—	0.2%/yr

BMI = body mass index; DIGAMI = Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction trial; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; IVAR = variable insulin group; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; VA CSDM = Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes Mellitus.

* Severe hypoglycemia is defined as an episode requiring third-party assistance.

Adapted with permission from *Can J Diabetes Care*.[54]

goal of <100 mg/dL (1 mg/dL = 0.02586 mmol/L) for those patients. The 2004 update of these guidelines suggested an optional LDL cholesterol goal of <70 mg/dL for patients with diabetes and CVD.[58,59]

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 increases 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.[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.[71,72,85] The recently published, large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[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.[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.[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 ($p = 0.026$).[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),[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).[88–90] The Diabetes Atherosclerosis Intervention Study (DAIS) trial[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),[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.[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[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

Table 4
Event rates in patients with diabetes mellitus in trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

Trial	Patients with Diabetes (N)	Event Rate (%)		RRR (%)	Event Definition
		Placebo/ Control	Statin/ Intervention		
Primary prevention					
WOSCOPS[78]	70	—	—	—	—
AFCAPS/TexCAPS[79]	155	8.4	4.8	43	Fatal and nonfatal MI, unstable angina, sudden death
ASCOT-LLA[80]	2,532	11.9	9.2	23	Total cardiovascular events*
CARDS[81]	2,838	2.5	1.5	37	Fatal CAD, nonfatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularization, and stroke
Secondary prevention					
4S[70]	202	45	22	51	Fatal CAD and nonfatal MI
CARE[71]	602	37	29	22	Fatal CAD, nonfatal MI, and revascularizations
LIPID[72]	782	23	19	17	Fatal CAD and nonfatal MI
Post CABG[73]	116	26	15	47	Cardiovascular death, nonfatal MI, nonfatal stroke, PCI, CABG
LIPS[74]	202	38	22	47	Cardiac death, nonfatal MI, PCI, CABG
PROVE-IT–TIMI 22[75†]	734	35	29	17	Death from any cause and major cardiovascular event[†]
TNT[87‡]	1,501	18	14	25	Fatal CAD, nonfatal MI, resuscitated cardiac arrest, or fatal or nonfatal stroke
Combined					
HPS[84]	5,963	25	20	20	Fatal CAD, nonfatal MI, fatal and nonfatal stroke, coronary and noncoronary revascularization
ALLHAT[86]	3,638	NR	NR	11	Fatal CAD and nonfatal MI
PROSPER[77]	623	18	23	−27[§]	Fatal CAD, nonfatal MI, fatal and nonfatal stroke

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events trial; 4S = Scandinavian Simvastatin Survival Study; HPS = Medical Research Council/British Heart Foundation Heart Protection Study; LIPID = Long-Term Intervention With Pravastatin in Ischaemic Disease trial; LIPS = Lescol Intervention Prevention Study; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; Post CABG = Post Coronary Artery Bypass Graft trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 trial; RRR = relative risk reduction; TNT = Treating to New Targets trial; WOSCOPS = West of Scotland Coronary Prevention Study.

* 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, PCIs, CABG, and stroke.

‡ TNT compared atorvastatin 10 mg/day as the control group with atorvastatin 80 mg/day as the intervention group.

§ 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.[93] However, recent studies suggest that there is no increased risk for myositis when fenofibrate is used in combination with a statin.[94]

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.[2,95] 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)[96] recommended beginning drug treatment in patients with diabetes with systolic blood pressure levels ≥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[97–101] describes the results of the clinical trials of blood pressure lowering in patients with diabetes. In a

Table 5
Event rates in patients with diabetes mellitus in fibrate trials

Population	Patients (N)	Event Rate (%)		RRR (%)	Event Definition
		Placebo	Fibrate		
HHS overall[88]	4,081	4.1	2.7	34	CAD death, nonfatal MI
HHS diabetes participants[88]	135	10.5	3.4	68	CAD death, nonfatal MI
DAIS[89]	418	24	18	23	Death, nonfatal MI, coronary revascularization, angina, hospitalization
VA-HIT overall[90]	2,531	22	17	23	CAD death, nonfatal MI, stroke
VA-HIT diabetes participants[90]	627	36	28	22	CAD death, nonfatal MI, stroke

CAD = coronary artery disease; DAIS = Diabetes Atherosclerosis Intervention Study; HHS = Helsinki Heart Study; MI = myocardial infarction; RRR = relative risk reduction; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

Table 6
Clinical trials of blood pressure (BP) lowering in patients with diabetes mellitus

Trial	Patients (N)	Duration (yr)	Mean BP (mm Hg)		Initial Therapy	Outcome	RRR
			Less Intensive	More Intensive			
SHEP[97]	583	5	155/72*	146/68*	Chlorthalidone	Stroke	22% (NS)
						CVD events	34%
						CAD	56%
Syst-Eur[98]	492	2	162/82	153/78	Nitrendipine	Stroke	69%
						CV events	62%
HOT[99]	1,501	3	148/85	144/81	Felodipine	CV events	51%
						MI	50%
						Stroke	30% (NS)
						CV mortality	67%
UKPDS[100]	1,148	8.4	154/87	144/82	Captopril or atenolol	Diabetes-related end points	34%
						Deaths	32%
						Stroke	44%
						Microvascular	37%
ABCD[101]	470	5.3	138/86	132/78	Nisoldipine or enalapril	C_{Cr}	NC
						Albuminuria	NC
						Retinopathy	NC
						Neuropathy	NC
						Mortality	49%
						MI, stroke, CHF	NS

ABCD = Appropriate Blood Pressure Control in Diabetes trial; CAD = coronary artery disease; C_{Cr} = creatine clearance; CHF = congestive heart failure; CV = cardiovascular; CVD = CV disease; HOT = Hypertension Optimal Treatment trial; MI = myocardial infarction; NC = no change; NS = not significant; RRR = relative risk reduction; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe trial; UKPDS = United Kingdom Prospective Diabetes Study.

* Courtesy of Sara Pressel, School of Public Health, University of Texas Health Science Center, Houston, Texas.

post hoc subgroup analysis of participants with type 2 diabetes in the Systolic Hypertension in the Elderly Program (SHEP),[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,[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,[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,[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% ($p = 0.009$).[100] 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.[101,103,104] 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[105] 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.[106] 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.[107] 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.[108]

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.[11,109,110] 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.[106,111] 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.[112,113] Aspirin is safe and effective across a dose range of 75–325 mg/day.[11,111] 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[114] 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.[113] 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.[14] 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.[114–116] On the basis of this evidence, ACE inhibitors can be recommended for reducing cardiovascular morbidity and mor-

Table 7
Action to Control Cardiovascular Risk in Diabetes (ACCORD) double 2 × 2 factorial design: observed distribution of participants

Glycemia Trial	BP Trial		Lipid Trial*		Total
	SBP <120 mm Hg	SBP <140 mm Hg	Group A	Group B	
HbA_{1c} <6.0%	1,178	1,193	1,383	1,374	5,128
7.0% ≤HbA_{1c} ≤7.9%	1,184	1,178	1,370	1,391	5,123
Subtotals	2,362	2,371	2,753	2,765	
Trial totals	4,733		5,518		10,251

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic BP.
* Treatment group assignments are blinded until the end of the trial.

tality in patients who have experienced acute MI, congestive heart failure, and nephropathy and in patients with type 2 diabetes with ≥1 additional risk factor for CVD.

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 HbA_{1c} target of <6.0%. Patients randomized to the standard group have an HbA_{1c} target of 7.0%–7.9%, with an expectation that the median HbA_{1c} 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.

1. Savage PJ. Cardiovascular complications of diabetes mellitus: what we know and what we need to know about their prevention. *Ann Intern Med* 1996;124(pt 2):123–126.
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–444.
3. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;241:2035–2038.

4. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. *BMJ* 1983;287:867–870.
5. Barrett-Connor E, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; 265:627–631.
6. Goldbourt U, Yaari S, Medalie JH. Factors predictive of long-term coronary heart disease mortality among 10059 male Israeli civil servants and municipal employees: a 23 year mortality follow-up in the Israeli Ischemic Heart Disease Study. *Cardiology* 1993;82:100–121.
7. Manson JE, Coldlitz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Int Med* 1991;151:1141–1147.
8. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–234.
9. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Stern MS, Boyko EJ, Reiber GE, Bennett PH, eds. *Diabetes in America*. 2nd ed. Washington, DC: National Institutes of Health, 1995: 429–448.
10. Morrish NJ, Stevens LK, Fuller JH, Keen H, Jarrett RJ. Incidence of macrovascular disease in diabetes mellitus: the London follow-up to the WHO Multinational Study of Vascular Disease in Diabetics. *Diabetologia* 1991;34:584–589.
11. ETDRS [Early Treatment of Diabetic Retinopathy Study] Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment of Diabetic Retinopathy Study report 14. *JAMA* 1992;266:1292–1300.
12. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Eight to nine year mortality in known non-insulin dependent diabetes and controls. *Kidney Int* 1992;42:731–735.
13. Neil A, Hawkins M, Potok M, Thorogood M, Cohen DA, Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes Care* 1993;16:996–1003.
14. HOPE [Heart Outcomes Prevention Evaluation] Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259.
15. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999;281:1291–1297.
16. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB Sr, Wilson PW, Savage PJ. Trends in cardiovascular complications of diabetes. *JAMA* 2004;292:2495–2499.
17. Booth GL, Kapral MK, Fung K, Tu JV. Recent trends in cardiovascular complications among men and women with and without diabetes. *Diabetes Care* 2006;29:32–37.
18. Behar S, Boyko EJ, Reicher-Reiss H, Goldbourt U. Ten year survival after acute myocardial infarction: comparison of patients with and without diabetes. *Am Heart J* 1997;133:290–296.
19. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ, for the GUSTO-1 [Global Utlization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] Investigators. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. *J Am Coll Cardiol* 1997;30:171–179.
20. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;102: 1014–1019.
21. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–393.
22. Moss SE, Klein R, Klein BEK, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 1994;154:2473–2479.
23. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 1994;43:960–967.
24. Andersson DKG, Svardsudd K. Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 1995;18:534–543.
25. Gall M-A, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving H-H. Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes* 1995;44:1303–1309.
26. Agewall S, Wikstrand J, Ljungman S, Fagerberg B, for the Risk Factor Intervention Study Group. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. *Am J Cardiol* 1997;80:164–169.
27. Turner RC. The UK Prospective Diabetes Study: a review. *Diabetes Care* 1998;21(suppl):C35–C38.
28. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. *Diabetes Care* 1998;21:1167–1172.
29. Hadden DR, Patterson CC, Atkinson AB, Kennedy L, Bell PM, McCance DR, Weaver JA. Macrovascular disease and hyperglycaemia: 10-year survival analysis in type 2 diabetes mellitus. The Belfast Diet Study. *Diabet Med* 1997;14:663–672.
30. Fu CC, Chang CJ, Tseng CH, Chen MS, Kao CS, Wu TJ, Wu HP, Chiang LN, Chen CJ, Tai TY. Development of macrovascular diseases in NIDDM patients in northern Taiwan: a 4-yr follow-up study. *Diabetes Care* 1993;16:137–143.
31. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412.
32. Lehto S, Ronnemaa T, Haffner SM, Pyorala K, Kallio V, Laakso M. Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 1997;46: 1354–1359.
33. Gerstein HC, Malmberg KA, Capes S, Yusuf S. Cardiovascular diseases. In: Gerstein HC, Haynes RB, eds. *Evidence-Based Diabetes Care*. Hamilton, Ontario, Canada: BC Decker, 2001: 488–514.
34. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141: 421–431.
35. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999;22:233–240.
36. Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. *J Am Coll Cardiol* 1999;33:612–619.
37. Gerstein HC, Yusuf S. Dysglycaemia and risk of cardiovascular disease. *Lancet* 1996;347:949–950.
38. Gerstein HC. Glucose: a continuous risk factor for cardiovascular disease. *Diabet Med* 1997;14(suppl):S25–S31.
39. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 1998;21:360–367.
40. Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a

22-year follow-up of healthy nondiabetic men. *Diabetes Care* 1999;22:45–49.
41. Haffner SM. The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease. *Endocr Rev* 1998;19: 583–592.
42. Gerstein HC, Capes SE. Dysglycemia: a key cardiovascular risk factor. *Semin Vasc Med* 2002;2:165–174.
43. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. *Ann Intern Med* 2004;141:413–420.
44. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853.
45. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352: 854–865.
46. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28:103–117.
47. Abraira C, Colwell JA, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. *Arch Intern Med* 1997;157:181–188.
48. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin I. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57–65.
49. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, et al, for the DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; 26:650–661.
50. Genuth S. Exogenous insulin administration and cardiovascular risk in NIDDM and IDDM. *Ann Intern Med* 1996;124:104–109.
51. Lawson M, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Care* 1999;22(suppl):B35–B39.
52. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;99:2626–2632.
53. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653.
54. Gerstein HC, Capes S. Advantages and perceived disadvantages of insulin therapy for patients with type 2 diabetes. *Can J Diabetes Care* 1999;23(suppl):S93–S96.
55. Smits P, Thien T. Cardiovascular effects of sulphonylurea derivatives: implications for the treatment of NIDDM? *Diabetologia* 1995; 38:116–121.
56. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999;131:281–303.
57. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.
58. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, for the National Heart, Lung, and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–239.
59. Grundy SM. Diabetes and coronary risk equivalency: what does it mean? *Diabetes Care* 2006;29:457–460
60. Sigurdsson G, Nicoll A, Lewis B. Metabolism of very low density lipoproteins in hyperlipidemia: studies of apolipoprotein B kinetics in man. *Eur J Clin Invest* 1976;6:167–177.
61. Kissebah AH, Alfarsi S, Evans DJ, Adams PW. Integrated regulation of very-low-density lipoprotein triglyceride and apolipoprotein-B kinetics in non-insulin-dependent diabetes mellitus. *Diabetes* 1982;31: 217–225.
62. Ginsberg H, Grundy SM. Effect of caloric restriction on very low density lipoprotein triglyceride metabolism in subjects with diabetes mellitus. *Diabetologia* 1982;23:421–425.
63. Howard BV, Reitman JS, Vasquez B, Zech L. Very-low density lipoprotein triglyceride metabolism in non-insulin-dependent diabetes mellitus: relationship to plasma insulin and free fatty acids. *Diabetes* 1983;32:271–276.
64. Ginsberg HN. Lipoprotein physiology in nondiabetic and diabetic states. *Diabetes Care* 1991;14:839–855.
65. Hollenbeck CB, Chen Y-D, Greenfield MS, Lardinois CK, Reaven GM. Reduced plasma high density lipoprotein-cholesterol concentrations need not increase when hyperglycemia is controlled with insulin in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1986;62:605–608.
66. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. Diabetes blood lipids and the role of obesity in coronary heart disease risk for women: the Framingham study. *Ann Intern Med* 1977;87: 393–397.
67. Feingold KR, Grunfeld C, Pang M, Doerrler W, Krauss RM. LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes. *Arterioscler Thromb* 1992;2:1496–1502.
68. Reaven GM, Chen Y-D, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoprotein particles. *J Clin Invest* 1993;92:141–146.
69. LRC-CPPT Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351–364.
70. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344: 1383–1389.
71. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E, for the CARE Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998; 98:2513–2519.
72. The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–1357.
73. Hoogwerf BJ, Waness A, Cressman M, Canner J, Campeau L, Domanski M, Geller N, Herd A, Hickey A, Hunninghake DB, Knatterud GL, White C. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. *Diabetes* 1999;48:1289–1294.

74. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B, for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215–3222.
75. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504.
76. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435.
77. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, et al, for the PROSPER [Prospective Study of Pravastatin in the Elderly at Risk] Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–1630.
78. WOSCOPS Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998;97:1440–1445.
79. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS [Air Force/Texas Coronary Atherosclerosis Prevention Study]. *JAMA* 1998;279:1615–1622.
80. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157.
81. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, for the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696.
82. Vijan S, Hayward RA, for the American College of Physicians. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. *Ann Intern Med* 2004;140:650–658.
83. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, for the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [published correction appears in *Lancet* 2005;366:1358]. *Lancet* 2005;366:1267–1278.
84. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
85. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;159:2661–2667.
86. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2998–3007.
87. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, Larosa J, Grundy S, Waters D. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226.
88. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–1245.
89. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001;357:905–910.
90. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410–418.
91. BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000;102:21–27.
92. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, et al, for the FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD [Fenofibrate Intervention and Event Lowering in Diabetes] study): randomised controlled trial. *Lancet* 2005;366:1849–1861.
93. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585–2590.
94. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI [Simvastatin Plus Fenofibrate for Combined Hyperlipidemia] trial). *Am J Cardiol* 2005;95:462–468.
95. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS [United Kingdom Prospective Diabetes Study] 36): prospective observational study. *BMJ* 2000;321:412–419.
96. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;157:2413–2446.
97. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, et al, for the Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886–1892.
98. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Autikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R, for the Systolic Hypertension in Europe Trial Investigators. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. 1999;*N Engl J Med* 340:677–684.
99. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose

aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755–1762.
100. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 1998;317:703–713.
101. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645–652.
102. Zanchetti A, Hansson L, Clement D, Elmfeldt D, Julius S, Rosenthal T, Waeber B, Wedel H, for the HOT [Hypertension Optimal Treatment] Study Group. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? *J Hypertens* 2003;21:797–804.
103. Schrier RW, Estacio RO, Jeffers B. Appropriate Blood Pressure Control in NIDDM (ABCD) trial. *Diabetologia* 1996;39:1646–1654.
104. Estacio RO, Jeffers BW, Gifford N, Schrier RW. The effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; 23(suppl):B54–B64.
105. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S, for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165:1410–1419.
106. American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus [position statement]. *Diabetes Care* 2003;26(suppl):S51–S61.
107. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR, for the United Kingdom Prospective Diabetes Study Group. Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998;316:823–828.
108. American Diabetes Association. Smoking and diabetes. *Diabetes Care* 2003;26(suppl):S89–S91.
109. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106.
110. Johnson ES, Lanes SF, Wentworth CE, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med* 1999;159:1248–1253.
111. Steering Committee of the Physicians' Health Study Research Group. Final report of the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–135.
112. American Diabetes Association. Aspirin therapy in diabetes [position statement]. *Diabetes Care* 2003;26(suppl):S87–S88.
113. Colwell JA. Aspirin therapy in diabetes [technical review]. *Diabetes Care* 1997;20:1767–1771.
114. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–153.
115. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 1996;156:286–289.
116. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1998;128:982–988.
117. ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007; 99(suppl):21i–33i.

Appendix

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