Diabetes mellitus is not merely a disorder of carbohydrate metabolism, but a cause of vascular disease affecting nearly all blood vessel types and sizes. Indeed, vascular complications are responsible for most of the morbidity, hospitalizations, and death that occur in patients with diabetes mellitus.1

Epidemiology

More than 29 million Americans, or nearly 10% of the United States population, have diabetes mellitus.3 The prevalence of diabetes mellitus increased significantly from 1980 to 2012 and associated closely with an increase in the number of overweight and obese persons.3,4 Of >660,000 patients in the National Health Interview Survey, the prevalence of diabetes mellitus in the United States increased from 3.5 per 100 persons in 1990 to 8.3 per 100 persons in 2012.4 Those who were Hispanic or with a high school education or less had a significantly greater rate of developing diabetes mellitus. Notably, over just the last 4 years of the survey, the incidence of new diabetes mellitus decreased from a peak of 8.8 per 1000 persons to 7.1 per 1000 persons, but the prevalence remained stable at 8.3 per 100 persons. Similarly, in the Framingham study, incidence of diabetes mellitus, although markedly elevated compared with observations from the 1970s, has recently stabilized, despite the increasing population weight burden.3 More recent work has implicated novel genetic associations and suggest future translational research targets in the understanding of this disease.5,6

The increasing prevalence of diabetes mellitus extends beyond the United States and is a global phenomenon. The
Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group estimates that the prevalence of diabetes mellitus increased from 153 million in 1980 to 347 million in 2008.7 The highest prevalence of diabetes mellitus is in Oceania, North Africa, the Middle East, and the Caribbean, each with an age-standardized prevalence of diabetes mellitus of 21% to 25% in men and 21% to 32% in women.7 Improvement of economic conditions, better living standards, and adoption of the adverse lifestyle habits of wealthier nations has levied a cost in terms of disease prevalence. For example, in China, the prevalence of diabetes mellitus increased from 2.3% in 1994 to 9.7% in 2008. The geographic distribution of diabetes mellitus in China closely follows the per capita gross regional product, with higher gross regional products associated with a higher prevalence of diabetes mellitus.8 In addition, the prevalence of diabetes mellitus is growing faster in urban compared with rural settings. This pattern has been noted in West African populations9 and India10 as well. Thus, as economic development continues, it is likely that the global diabetes mellitus pandemic will worsen.

Along with a greater prevalence of diabetes mellitus comes a heightened risk of vascular disease, which affects the microvasculature, arteries, and veins. This review will discuss the impact of diabetes mellitus on these circulatory components, making clear the importance of vascular disease in diabetes mellitus.

Microvascular Disease
There are 3 major manifestations of microvascular disease, retinopathy, nephropathy, and neuropathy, that will be reviewed.

Retinopathy
Microvascular disease is strongly associated with hyperglycemia. Over the range of chronic hyperglycemia commonly seen in practice, there is an 11-fold increase in retinopathy compared with a 2-fold increase in coronary artery disease.11 Despite the importance of hyperglycemia, some patients may develop early evidence of retinopathy as long as 7 years before the development of frank type 2 diabetes mellitus, indicating a contribution of insulin resistance. In addition to severity of hyperglycemia and duration of diabetes mellitus, other factors associated with retinopathy include hypertension, smoking, and dyslipidemia. These and other pathophysiologic mechanisms, including insulin resistance and inflammation, may contribute to the microvascular disease process.12

The earliest histopathologic sign of diabetes mellitus–related retinopathy is a loss of pericytes. Pericytes wrap around the arteriolar and capillary endothelial cells and participate in maintenance of capillary tone, growth, and resistance to damage from oxidative stress.13,14 The disease is then marked by basement membrane thickening, endothelial cell permeability, and the formation of microaneurysms.15 Broadly, there are 2 types of retinopathy, nonproliferative (background) and proliferative. In nonproliferative retinopathy, patients may develop dot hemorrhages, which are small hemorrhages in the middle of the retina surrounded by hard lipid exudates. Retinal edema also may be seen. Proliferative retinopathy is the development of neovascularization on the retina, which can be complicated by vitreous hemorrhage. These latter changes, without treatment, can lead to vision impairment.

In an analysis of the National Health and Nutrition Survey, the prevalence of retinopathy in the diabetic population was 28.5%, and 4.4% of the total had threatened loss of vision. Male sex, higher glycosylated hemoglobin levels, longer duration of diabetes mellitus, higher blood pressure, and use of insulin all were associated with developing retinopathy.16 In a pooled analysis of 35 studies of diabetic people, collected from 1980 to 2008 from around the world, the prevalence among those 20 to 79 years old was 35% for any retinopathy, 7% for proliferative retinopathy, and 10% for vision-threatening retinopathy.17 Patients of African or Caribbean descent have higher rates of retinopathy compared with Caucasians or south Asians.18 The presence of microvascular disease is also a marker of diffuse vascular disease. Diabetic patients with retinopathy have a higher rate of atherosclerosis than diabetic patients without retinopathy.19

Diabetic retinopathy is a leading cause of blindness in the United States. It was responsible for ~8% of cases of legal blindness and 12% of all new cases of blindness in the United States each year in the last decade of the twentieth century.20 However, new treatments have improved outcomes with a significantly reduced rate of severe visual impairment. Despite the increase in diabetes mellitus over the last few decades and a commensurate increase in the number of patients with diabetic retinopathy to ~4 to 5 million people in the United States, the number of patients with diabetes mellitus with visual impairment has decreased from 26% in 1997 to ~19% in 2011,21 whereas the overall rate of visual impairment in the civilian population has remained stable at 9.3%.

Systemic medical therapy has played an important role for microvascular disease and will be discussed later. There are 2 treatments specific to the eye, which have reduced the progression to blindness. Two clinical trials, the Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study, established macular and pan-retinal photocoagulation as primary therapy for these 2 ocular complications.22,23 More recently, the use of injected vascular endothelial growth factor...
Neuropathy
The development of diabetic neuropathy is associated with vascular and nonvascular abnormalities. In addition to basement membrane thickening and pericyte loss, there is evidence of decreased capillary blood flow to C fibers, resulting in attenuated perfusion of the nerves and attendant endoneurial hypoxia. The neuropathy is characterized by axonal thickening and eventual loss of neurons.

Diabetic neuropathy can vary widely, although there are two major types. The most common is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy, which is associated with severity and duration of hyperglycemia. The pathophysiology of this subtype is similar to the other microvascular manifestations of diabetes mellitus. Less common are polyneuropathies that develop at more unpredictable times during the course of diabetes mellitus that may not be symmetrical. The polyneuropathies commonly present with pain or autonomic symptoms and the course may be fluctuating.

Medical Therapy and Microvascular Disease
Clinical trials have demonstrated that microvascular disease may be prevented or its progression attenuated through aggressive treatment of hyperglycemia and the cardiovascular risk factors. The seminal trial in glycemic control is the Diabetes Control and Complications Trial (DCCT). In the DCCT, 1441 type 1 diabetic patients, 726 without retinopathy and 715 with mild retinopathy, were randomly assigned to intensive or routine glycemic control and followed over 7 years, and as many as 25% of patients with type 2 diabetes mellitus have evidence of neuropathy by 10 years after the diagnosis is made. The prevalence is significantly worse in Asia. In a study of 5549 patients with type 2 diabetes mellitus across 103 medical centers in 10 Asian nations or regions, 40% had microalbuminuria and 19% had macroalbuminuria. One contributor may be poor risk factor control because <12% met blood pressure goal levels, and the mean Hgb A1c was 7.8%. In 2011 in the United States, nearly 50,000 patients with diabetes mellitus began treatment for renal failure and >225,000 required either dialysis or a kidney transplant.

Neuropathy
Intensive treatment was associated with a 76% reduction in the development of retinopathy and a 56% reduction in the need for laser therapy in the patients with mild retinopathy at baseline. Similarly, intensive therapy reduced the rate of microalbuminuria by 43% and neuropathy by 69%. The benefits of glucose lowering also have been demonstrated in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study (UKPDS). More aggressive glycemic control of glucose was studied in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials. In both trials, the intensive arm was treated to a target glycohemoglobin of =6.5%, with modest benefits in some but not all markers of microvascular disease, which were inadequate to change goals of glycemic treatment.

Blood pressure control also may reduce the likelihood of microvascular disease. A recent meta-analysis examined the impact of blood pressure control on diabetic retinopathy. It found that better blood pressure control resulted in an 18% reduction in the incidence of retinopathy in patients with type 1 diabetes mellitus and a 22% reduction in patients with type 2 diabetes mellitus. In contrast, no benefit was noted in preventing the progression of retinopathy. For neuropathy, certain blood pressure agents are more effective. Angiotensin-converting enzyme inhibitors (ACEIs) reduce the incidence of neuropathy, as determined by albuminuria, by ≈30%. ACEIs are also superior to calcium channel blockers, despite no significant difference in blood pressure lowering. In contrast, the data supporting the efficacy of angiotensin receptor blockers is mixed, with more recent data less positive than early studies.

In contrast to the benefits noted in atherosclerotic cardiovascular disease, statins do not reduce the development of retinopathy, possibly because these increase levels of vitreous vascular endothelial growth factor. Statins do not affect either neuropathy or neuropathy. Interestingly, fibrates may reduce the development of microvascular disease. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, patients randomly allocated fenofibrate had a decrease in albuminuria progression and retinopathy requiring laser therapy. A subsequent retrospective evaluation similarly found a 22% reduction in diabetic retinopathy with fibrate treatment.

Cardiovascular Disease
Coronary Artery Disease
The linkage between diabetes mellitus and macrovascular disease was made >40 years ago, with the heightened risk of myocardial infarction (MI) and cardiovascular death shown in several different populations. The appreciation of the impact of diabetes mellitus on cardiovascular disease was increased substantially when it was reported in a Finnish population study that diabetes mellitus alone carried the same risk of future MI and cardiovascular death as patients without diabetes mellitus but a previous MI. The effect of this finding was to render, at the time, the status of diabetes mellitus as an MI risk equivalent by the Adult Treatment Panel 3 of the National Cholesterol Education Program and thus for diabetic
patients to receive secondary prevention level treatment.\textsuperscript{53} The status of diabetes mellitus, per se, as a risk equivalent to prior MI has been modified recently. In a large meta-analysis of >45,000 patients with follow up as long as 25 years, the risk of coronary heart disease events was \( \approx 40\% \) lower in the diabetes mellitus but no prior MI patients compared with the patients with a prior MI and no diabetes mellitus.\textsuperscript{54} One way to understand the difference in risks between the Finnish study\textsuperscript{52} and the meta-analysis is to examine the definitions of the study population. In the Finnish study, the definition of type 2 diabetes mellitus was based on diagnostic criteria from the 1980s, with higher requirements for glucose levels needed for diagnosis. The mean glycosylated hemoglobin was \( >10\% \), and \( >50\% \) of the diabetic population had baseline atherosclerotic disease, but only \( \approx 15\% \) had a prior MI.\textsuperscript{55} Later studies adhered to the lower thresholds of glucose\textsuperscript{56} to make the diagnosis and would, therefore, include lower-risk patients.

Although diabetes mellitus alone is not the risk equivalent of prior myocardial infarction for future myocardial infarction, diabetes increases the risk of future MI more than any other risk factor, save cigarette smoking. In the INTERHEART global case–control study of >27,000 patients, diabetes mellitus increased the risk of MI more in women than any other risk factor.\textsuperscript{57} Indeed, the increasing prevalence of diabetes mellitus is likely to offset, in part, population improvement in other risk factors and ensure an ongoing burden of coronary heart disease.\textsuperscript{58} Just a decade ago, in a study of 4,196 purportedly nondiabetic patients with coronary disease from 25 nations, oral glucose tolerance testing revealed that 18\% had undiagnosed diabetes mellitus, 32\% had impaired glucose tolerance, and 5\% had impaired fasting glucose.\textsuperscript{59} Thus, more than half of all patients had evidence of the dysmetabolic state associated with type 2 diabetes mellitus. In the Nationwide Inpatient Sample, the prevalence of diabetes mellitus in the 1.5 million patients presenting with acute MI increased from 22.2\% in 2000 to 29.2\% in 2009.\textsuperscript{60}

The consequences of MI are greater in patients with diabetes mellitus compared with those without it. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50 Trial that investigated the effect of vorapaxar in patients with recent MI, patients with diabetes mellitus suffered a near 2-fold greater risk of cardiovascular death, MI, or stroke than nondiabetic patients.\textsuperscript{61} Similarly, in the Platelet Inhibition and Patient Outcomes (PLATO) trial, which compared ticagrelor to clopidogrel in patients with acute coronary syndromes, patients with diabetes mellitus were 66\% more likely to develop cardiovascular death, MI, or stroke.\textsuperscript{62} Once diabetic patients undergo percutaneous coronary revascularization, their outcomes are worse as well. In a study of 28,849 Veterans Affairs patients who received a drug-eluting stent, the 1-year event rate for MI was 7.6\% for diabetic patients requiring insulin, 5.4\% in diabetic patients not requiring insulin, and 4.4\% in nondiabetic patients.\textsuperscript{63} The need for revascularization over the first year of follow-up was 17.3\%, 14.8\%, and 11.7\% respectively. In 2 recent trials of everolimus-eluting stents, the outcomes of death, MI, and stroke were significantly higher in the patients with diabetes mellitus compared with those without diabetes mellitus.\textsuperscript{64,65}

Among asymptomatic patients with diabetes mellitus, screening for myocardial ischemia or anatomic evidence of coronary artery disease does not seem to affect outcomes, despite a worse cardiovascular prognosis compared with nondiabetic persons. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1,123 asymptomatic patients with type 2 diabetes mellitus were randomly assigned to an adenosine-stress myocardial perfusion imaging or no screening.\textsuperscript{66} Over the course of nearly 5 years of follow-up, there was no significant difference in the primary end point of cardiac death and MI. In the Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64 (FACTOR-64) study, 900 patients with type 1 or 2 diabetes mellitus were randomly assigned to coronary artery disease screening with coronary computed tomography angiography or not.\textsuperscript{67} Both groups, as in DIAD, received therapy according to national guidelines. Over the course of 4 years of follow-up, the composite of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization did not differ between groups. In FACTOR-64, 94\% of the patients who were screened had no evidence of coronary artery disease.

Despite the persistently higher rate of coronary heart disease events in diabetic compared with nondiabetic patients, cardiovascular events have dropped precipitously over the last 2 decades (Figure). In the National Hospital Discharge Survey, the prevalence of acute MI in patients with diabetes mellitus decreased from 141 per 10,000 persons in 1990 to 45.5 per 10,000 persons in 2010, representing a 68\% decline.\textsuperscript{68} These improvements are likely related to more frequent use of effective medical and revascularization strategies. Indeed, differences in the use of well-proved therapies have been associated with better outcomes after acute MI in Sweden compared with the United Kingdom, despite a greater prevalence of diabetes mellitus in Sweden.\textsuperscript{69} The presence of diabetes mellitus affects the type of revascularization needed in severe coronary artery disease. Randomized clinical trial have shown that patients with diabetes mellitus and extensive coronary disease requiring revascularization have better outcomes with coronary artery bypass grafting than percutaneous coronary intervention (PCI).\textsuperscript{70} Two clinical trials have addressed this question. In a subgroup of the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial, diabetic patients with the highest SYNTAX risk score had a significantly improved survival when treated with coronary artery bypass grafting compared with PCI, whereas this finding was not noted in nondiabetic patients.\textsuperscript{71} The benefit of coronary artery bypass grafting compared with PCI in diabetic patients was compared directly in the recent the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial. This trial compared revascularization strategies in diabetic patients, 83\% of whom had 3-vessel coronary artery disease. In FREEDOM, the 5-year rate of death, MI, and stroke was 26.6\% in the PCI arm and 18.7\% in the coronary artery bypass grafting arm.\textsuperscript{72} Diabetes mellitus severity, as described by the need for insulin treatment, increased the risk of overall death/MI/stroke rates.\textsuperscript{73} These data suggest that among patients with severe coronary artery
disease, those with diabetes mellitus require more complete revascularization, as would more likely occur with coronary bypass surgery than PCI, than do nondiabetic patients.

**Stroke**

Associating diabetes mellitus with the risk of stroke is complex because of the variety of stroke types. In the Nurses Health Study of 116,316 women aged 30 to 55 years followed for 26 years, type 1 diabetes mellitus was associated with increased risk of both ischemic and hemorrhagic strokes, whereas type 2 diabetes mellitus increased the risk of ischemic stroke but not hemorrhagic stroke. Similarly, in a survey of 40,000 Asian patients, type 2 diabetes mellitus associated with increased risk of ischemic but not hemorrhagic stroke. Interestingly, metabolic disturbances may play an important role. Recent studies have suggested that the risk of stroke is increased in diabetic patients with hyperglycemia, but not in those without hyperglycemia. The relationship of the metabolic syndrome is more complex. The risk of first stroke doubles with the presence of the metabolic syndrome, but recurrent stroke is not affected.

Diabetes mellitus worsens the outcomes from stroke, as it does in coronary artery disease. A study of nearly 12,000 community-dwelling men in western Australia found that diabetes mellitus significantly increased the risk of death in patients with stroke. Moreover, the duration of diabetes mellitus was a significant cofactor, suggesting a dose–response relationship of diabetes mellitus exposure to stroke severity. These observations are similar to those reported in a German nationwide health insurance study and a Veterans Affairs investigation. Diabetic patients also have a higher rate of neurological deterioration compared with nondiabetic patients after an acute ischemic stroke and do worse than nondiabetic patients even for strokes of the same size and severity.

Thrombolysis is a beneficial treatment for acute ischemic stroke in patients with diabetes mellitus, though outcome after thrombolysis may be worse than in nondiabetic patients. In a study of 389 men with stroke treated with intra-arterial thrombolysis, diabetes mellitus status and admission glucose level did not affect recanalization rates, but still were predictors of poor outcome, suggesting an impact of diabetes mellitus on the nonvascular components of stroke pathology as well.

**Peripheral Artery Disease**

Like the other manifestations of atherosclerosis, peripheral artery disease (PAD) is linked strongly to diabetes mellitus. Several large epidemiological surveys have demonstrated a 2- to 4-fold increase in the risk of developing PAD, as determined by an ankle–brachial index ≤0.90. In the German Epidemiological Trial on Ankle Brachial Index study, 26.3% of the patients with diabetes mellitus developed PAD compared with 15.3% of the nondiabetic patients, and diabetes mellitus increased the risk of PAD to a greater extent than it did for CAD or stroke. Diabetes mellitus also increases the rate of disease development in younger patient groups. In the Chicago Healthy Aging Study, diabetes mellitus increased the rate of PAD by >7-fold during the 39 year follow-up period.

In patients with diabetes mellitus, detecting PAD may present challenges. Diabetes mellitus is associated with medial calcinosis, which may artifactually raise the ankle–brachial index because of noncompresibility of leg arteries, despite significant artery occlusive disease and reductions in the actual ankle perfusion pressure. For patients for whom there is a high suspicion of PAD, a toe–brachial index may be obtained, which is less likely to be affected by vascular calcification. Here, a toe–brachial index <0.7 is diagnostic of PAD.

Diabetes mellitus adversely affects lower extremity functional capacity too. In a cross-sectional study of 460 patients, participants with diabetes mellitus and PAD were more likely than nondiabetic persons to have neuropathy, exertional leg symptoms, and pain at rest. In another study, diabetes mellitus increased the likelihood of pain on exertion, atypical leg pain, or pain at rest by 2-fold and decreased the likelihood that the leg pain would be above the calf. In a retrospective cohort analysis of adults with commercial, Medicare supplemental

![Figure. Trends in age-standardized rates of diabetes mellitus–related complications, 1990 to 2010.](http://circres.ahajournals.org/)

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**Population with Diabetes**

- **Acute myocardial infarction**
- **Stroke**
- **Amputation**
- **ESRD**
- **Death from hyperglycemic crisis**

<table>
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<tr>
<th>Events per 10,000 Adult Population with Diagnosed Diabetes</th>
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<th>1995</th>
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<th>2010</th>
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<td>125</td>
<td>100</td>
<td>75</td>
<td>50</td>
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<tr>
<td>Amputation</td>
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<td>50</td>
<td>25</td>
<td>20</td>
<td>10</td>
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<tr>
<td>ESRD</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Death from hyperglycemic crisis</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
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*Figure.* Trends in age-standardized rates of diabetes mellitus–related complications, 1990 to 2010.
or Medicaid health Insurance from 2003 to 2008, there was a mean annualized prevalence of critical limb ischemia of 1.33% and a more than doubling of that rate among patients with diabetes mellitus.97 Diabetes mellitus is not associated with a progressive decline in ankle perfusion pressure over time,98 but patients with diabetes mellitus are at a 4-fold risk of amputation at every level of ankle perfusion pressure as measured by the ankle–brachial index compared with patients without diabetes mellitus.99 For patients who undergo revascularization, the graft outcomes are similar to nondiabetic patients.100 In the 2 largest randomized controlled trials conducted in patients with critical limb ischemia, The Project or Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) III Study and Bypass versus Angioplasty in Severe Ischemia of the Leg, diabetes mellitus was not associated with loss of graft patency.101–103 Despite successful revascularization, patients with diabetes mellitus are less likely to walk and more likely to suffer amputation. In a study of 1000 consecutive patients who underwent revascularization for critical limb ischemia, diabetes mellitus portended a 40% higher rate of deterioration of ambulatory status after the procedure.104 In a population-based cohort of linked nationwide databases in Sweden of 1840 patients, amputation rates were 65% higher over the course of 2.2 years after lower extremity bypass surgery for critical limb ischemia in patients with diabetes mellitus compared with those without diabetes mellitus.105

Patients with diabetes mellitus have other conditions that contribute to foot wounds and exacerbate the complications of vascular insufficiency, such as neuropathy and altered foot mechanics. The presence of these additional complications may make determination of the pathogenesis of pedal ulcers more difficult to ascertain. Therefore, particular care is required to determine the contribution of both vascular insufficiency and neuropathy when a treatment plan is created. Nonvascular therapies, including protective foot care, wound care, and frequent inspection, are important in limb preservation.

Medical Therapy of Diabetes Mellitus and Atherosclerosis

Despite increasing incidence and prevalence of diabetes mellitus in the population, improvements in therapeutic interventions have reduced the risk of adverse cardiovascular outcomes.106 In 1990, there were 178 million adults in the United States, 6.5 million patients with diabetes mellitus and 140,000 diabetic patients had an MI. In 2010, there were 226 million adults in the United States, 207,000,000 with diabetes mellitus and 135,700 patients with an MI. Over time, despite the increase in number of patients with diabetes mellitus, the cardiovascular event rate has decreased significantly. This can be seen by reductions in the rate of MI (~68%), stroke (~53%), and amputation (~51%).108 The decline in the rate of adverse cardiovascular events likely results, at least in part, from medical therapy for blood pressure, lipids, platelet activation, and hyperglycemia (Table).

Hypertension

Of treatments for cardiovascular risk factors, therapy for hypertension was the first associated with a reduction in mortality. The UKPDS study established that blood pressure control to a level of 144/82 reduced stroke by 44% and diabetes mellitus–related death by 32%.106 The UKPDS study also compared the use of captopril and atenolol as first-line agents, finding no difference between these groups.107 It should be noted that the majority of patients needed either 2 or 3 medications for control, rendering conclusions about comparative effectiveness difficult.

The Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure had recommended that hypertensive patients with diabetes mellitus should have their blood pressure lowered to 130/80 mm Hg.108 In the ADVANCE trial, 1140 patients with type 2 diabetes mellitus were randomly given the combination of perindopril/indapamide or placebo in addition to current therapy, irrespective of initial blood pressure.109 In this trial, mean blood pressure at entry was 145/81 mm Hg. In the active treatment compared with the placebo group, blood pressure was reduced by 5.6/2.2 mm Hg. All-cause mortality was reduced by 14%. In an observational subgroup analysis of diabetic patients with coronary artery disease in the International Verapamil SR-Trandolapril Study, all-cause mortality was similarly reduced when systolic blood pressure was tightly controlled to <130 mm Hg or to usual control of <140 mm Hg compared with uncontrolled blood pressure >140 mm Hg.110 As the reduction in mortality was similar with systolic blood pressure lowering to <130 and <140 mm Hg, the ACCORD trial tested the hypothesis that lowering blood pressure to an even lower level may provide additional benefit.111 In this trial, 4733 type 2 diabetic subjects were randomly allocated intensive therapy, targeting a systolic pressure <120 mm Hg, or standard therapy, targeting a systolic pressure <140 mm Hg. Over the course of nearly 5 years of follow up, there was no significant difference in the rate of cardiovascular death, nonfatal MI, and nonfatal stroke. To achieve the target blood pressure, subjects required an average of nearly 1.5 more medications. These data suggest that lowering blood pressure <140/90 mm Hg remains a reasonable target.

In contrast to the impact of aggressive blood pressure lowering in patients with diabetes mellitus, the Systolic Blood Pressure Intervention Trial (SPRINT) evaluated an aggressive approach in 9361 nondiabetic subjects with an SBP of 130 mm Hg or higher and increased cardiovascular risk.112 In contrast to ACCORD, there was a significant reduction in mortality in the group treated to an SBP of <120 mm Hg compared with the group treated to an SBP of <140 mm Hg that cause the trial to be stopped early. This trial used the same treatment strategy as ACCORD, and the direction of the outcomes was similar. It may be reasonable to suggest that ACCORD, with a patient population less than half the size of SPRINT, may not have had the power necessary in this population.113 However, it should be noted that there was a 27% reduction in death from any cause in SPRINT, but none noted in ACCORD. The recent data may not change SBP goals in patients with diabetes mellitus.

Several trials have examined the efficacy of inhibitors of the renin angiotensin system in particular for reducing atherosclerotic vascular events in patients with diabetes mellitus. In the Heart Outcomes Prevention Evaluation trial, 9297 subjects with atherosclerosis114 or diabetes mellitus115 and a risk factor
for atherosclerosis were randomized to the ACEI ramipril or placebo. The baseline blood pressure was <140/90 mm Hg. Ramipril decreased death, MI, and stroke in the diabetic subgroup. The efficacy of ACEI has been supported by the results of other large trials for cardiovascular risk reduction,109,116,117 in recurrent stroke prevention,118 and mortality after MI.119–121 The data supporting the use of angiotensin receptor blockers has been mixed.122–125 For example, in the Losartan Intervention For End point reduction in hypertension study, 1195 diabetic patients with hypertension complicated by left ventricular hypertrophy were included. The subjects given losartan had a significant reduction in the composite of cardiovascular death, stroke, or MI and in the total mortality alone. In contrast, in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study, 20332 patients, including 5743 with diabetes mellitus, were treated with telmisartan or placebo after recent ischemic stroke. The addition of telmisartan reduced neither stroke recurrence nor major cardiovascular events. Recently, an angiotensin receptor-neprilysin inhibitor was compared with enalapril in patients with reduced left ventricular function congestive heart failure. Cardiovascular outcomes were improved similarly in the diabetic and nondiabetic groups.126 The value of an angiotensin receptor-neprilysin inhibitor in treatment of diabetic patients with hypertension or for MI risk reduction is unknown.

**Dyslipidemia**

The use of the hydroxymethylglutaryl-CoA reductase inhibitors (statins) class of lipid treatments was established in diabetes mellitus with the reporting of the Heart Protection Study.127 In this trial of >20000 subjects, ≈6000 had diabetes mellitus without evidence of cardiovascular disease. Treatment with simvastatin 40 mg daily compared with placebo significantly reduced the rate of nonfatal MI or death, stroke, and revascularization.128 These benefits were substantiated in the Collaborative Atorvastatin Diabetes Study129 and the Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm.130 Statins are equally successful for secondary prevention of

<table>
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<th>Table. Medication Effect by Number Needed to Treat on Outcomes in Diabetes Mellitus</th>
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<td>Intervention</td>
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<tr>
<td>Sulfonylurea-Insulin</td>
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<td>Empagliflozin</td>
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BP indicates blood pressure; CHD death, sudden deaths ascribable to coronary heart disease, but for which an acute myocardial infarction could not be confirmed; CHF, congestive heart failure; Cor, coronary; CVA, stroke; CVD, cardiovascular death; F/NFCVA, fatal or nonfatal stroke; MI, myocardial infarction; NNT, number needed to treat; Revasc, revascularization; and UA, unstable angina.
cardiovascular events in patients with diabetes mellitus because significant reductions in cardiovascular events have been noted in diabetic patients with a history of coronary artery disease\textsuperscript{131,132} or stroke.\textsuperscript{52} The benefits of statins have not been demonstrated in patients with renal failure requiring hemodialysis.\textsuperscript{133,134}

Recently, it has been reported that statin administration is associated with an increase in incident diabetes mellitus\textsuperscript{135} and that familial hypercholesterolemia is associated with a decrease in diabetes mellitus prevalence.\textsuperscript{136} In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial study, the development of diabetes mellitus was accelerated by statins by \(5\) to \(6\) weeks, but did not mute the cardiovascular benefit of these agents in prediabetic patients.\textsuperscript{137} In a cross-sectional population-based study, the prevalence of type 2 diabetes mellitus was lower in carriers of apolipoprotein B mutations and those with low-density lipoprotein receptor mutations than in unaffected relatives.\textsuperscript{136} In the Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy (ODYSSEY LONG TERM) Study, alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9, reduced low-density lipoprotein by \(>60\%\), but had no effect on diabetes mellitus incidence or worsening out to a follow-up of \(78\) weeks.\textsuperscript{138} These findings suggest an interplay between lipids, their receptors, and glucose metabolism.

The efficacy of other lipid-lowering classes of drugs in people with diabetes mellitus is more limited. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial reported that the addition of ezetimibe \(10\) mg to simvastatin \(40\) mg was superior to simvastatin and placebo in \(18\,144\) patients who had been hospitalized for an acute coronary syndrome within the preceding \(10\) days.\textsuperscript{139} In the simvastatin/ezetimibe group, the achieved low-density lipoprotein level was \(53.7\,\text{mg/dL}\) compared with \(69.5\,\text{mg/dL}\) in the simvastatin alone group. There was a \(5\%\) relative and \(1.6\%\) absolute risk reduction in the rate of death, major coronary event, or nonfatal stroke with combination therapy. Subjects with diabetes mellitus had a statistically significantly better response to the addition of ezetimibe than subjects without diabetes mellitus. Several trials have evaluated the benefits of fibrates and niacin, but neither of these agents, as add-on therapy to statins, improved cardiovascular outcomes, with the exception of findings in one trial.\textsuperscript{46,140,141} In the FIELD trial, the rate of first amputation and minor amputation was reduced by fenofibrate, although major amputation was not.\textsuperscript{141}

**Hyperglycemia**

Until recently, it was unclear to most practitioners if glycemic control provides the same benefits in cardiovascular risk reduction as it does for microvascular risk reduction. Of the many hypoglycemic agents now available, metformin is most well-established in this area. In UKPDS, metformin treatment trended to reduce the risk of MI, but the decline in MI rate did not reach statistical significance. The benefit of metformin was also hard to interpret because of confounding findings. When it was added to a sulfonylurea, it increased mortality, but when administered to subjects \(>20\%\) above ideal body weight, there was a reduction in all-cause mortality.\textsuperscript{38,142} In the long-term follow-up study of UKPDS patients, those treated with metformin suffered one third fewer MIs and one quarter fewer deaths, despite similar glycemic control to other diabetes mellitus medications, after the active portion of the study ended.\textsuperscript{143} Other studies have supported the use of metformin, albeit in retrospective assessments rather than prospective trials.\textsuperscript{144,145}

For patients with type 1 diabetes mellitus, intensive glucose control was shown to modestly reduce cardiovascular events in the long-term follow-up to the DCCT trial of \(1441\) patients. In the Epidemiology of Diabetes Interventions and Complications Study, intensive treatment reduced the rate of nonfatal MI, stroke, and death by \(57\%\).\textsuperscript{146} However, the absolute reduction was small, with events occurring in \(52\) conventionally treated patients and \(31\) patients in the intensive arm over \(17\) years of follow-up.

Most other classes of hypoglycemic agents have not been found to reduce cardiovascular events. This includes the dipeptidyl peptidase-4 inhibitors,\textsuperscript{147,148} incretin mimetics, thiazolidinediones,\textsuperscript{149} nateglinide,\textsuperscript{150} and ranolazine.\textsuperscript{151} A recent study of the sodium glucose cotransporter-2 inhibitor, empagliflozin, did demonstrate improvement in cardiovascular outcomes. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients study, \(7020\) patients were randomly assigned to placebo or \(2\) doses of empagliflozin. Over the course of \(3\) years of follow-up, there was a \(2.2\%\) absolute and \(38\%\) relative reduction in death from cardiovascular causes, \(2.6\%\) absolute and \(32\%\) relative risk reduction in all-cause death, but also a nonsignificant increase in stroke in the patients treated with empagliflozin.\textsuperscript{152} Use of empagliflozin was associated with significant reductions in glycohemoglobin, blood pressure, weight, and waist size, so the lack of change or trend toward increase in stroke is curious and unexplained. The efficacy of this medication suggests that the mechanism of glucose lowering may be as, or more, important than targeted glucose lowering per se. The correct placement of this therapy in the hypoglycemic armamentarium is not established.

**Antiplatelet Therapy**

Despite experimental evidence of platelet activation in humans with type 1 or 2 diabetes mellitus,\textsuperscript{153} the efficacy of antiplatelet therapy in the absence of atherosclerosis is not established. Two recent clinical trials examined aspirin in patients with diabetes mellitus, but in neither could a benefit be demonstrated. In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, \(2539\) patients with diabetes mellitus and no history of atherosclerosis were randomly assigned to low-dose aspirin or no treatment.\textsuperscript{154} The primary end point of fatal and nonfatal heart events, fatal and nonfatal stroke events, and peripheral artery disease was not significantly different between the groups. Similarly, in the Prevention of Progression of Arterial Disease and Diabetes trial of \(1276\) patients with diabetes mellitus and peripheral artery disease diagnosed by an ankle brachial index \(<0.99\), low-dose aspirin did not significantly reduce the primary composite end point of death from coronary heart disease or stroke, nonfatal
MI or stroke, or amputation above the ankle for critical limb ischemia. The joint scientific statement by the American Diabetes Association, American Heart Association, and American College of Cardiology Foundation examined the primary prevention aspirin clinical trial literature and found nonsignificant reductions in heart attack and stroke. It stated that the use of low-dose aspirin is reasonable in patients with diabetes mellitus for primary prevention if there is a cardiovascular disease risk of >10% over 10 years.

The efficacy of drugs that inhibit adenine diphosphate receptor–mediated activation of platelets in primary prevention of patients with diabetes mellitus and no atherosclerosis is not known. In the clopidogrel versus aspirin in patients at risk of ischemic events trial, patients with a history of MI, stroke, or PAD were randomly allocated aspirin or clopidogrel. Among the 1914 participants with diabetes mellitus at study entry, the event rate of those allocated aspirin was 17.7% compared with 12.7% in the nondiabetic subjects. Clopidogrel reduced the absolute composite rate of vascular death, MI, stroke, and rehospitalization more in the diabetic subjects, with an absolute reduction of 2.1% and a relative risk reduction of 12.5% compared with an absolute reduction of 0.9% and relative risk reduction of 6.1% in patients without diabetes mellitus.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events trial demonstrated the benefit of adding clopidogrel to aspirin therapy both in diabetic and nondiabetic patients with an acute coronary syndrome. In the acute setting, more potent adenine diphosphate inhibitors seem to provide better results. In a trial of patients with acute coronary syndromes, prasugrel was more effective than clopidogrel in reducing a composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke, and the benefit was greater in diabetic than in nondiabetic patients. Ticagrelor was compared with clopidogrel in the PLATO trial and was found to be superior to clopidogrel. Diabetic subjects did not benefit more than nondiabetic subjects.

Recently, a new antiplatelet target has been identified and tested: the protease-activated receptor-1, the canonical receptor of thrombin. Vorapaxar, a protease-activated receptor-1 antagonist, has been tested in 2 clinical settings: acute coronary syndrome and recent MI, recent stroke, or PAD. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50 trial, 26,449 subjects with a history of MI, ischemic stroke, or PAD were randomized to vorapaxar or placebo and followed for a median of 30 months. In this study, the patients with a history of stroke were stopped early because of an increased rate of intracranial hemorrhage. In the MI and PAD cohorts, there was a significant 16% reduction in death from cardiovascular causes, MI, or stroke. The benefit for patients with diabetes mellitus and a history of MI was significantly greater than in patients without diabetes mellitus, with a 27% relative risk reduction. As a result, vorapaxar is now an approved medication for patients with a history of MI or PAD, but contraindicated in patients with a history of stroke. Its role in routine practice is in development.

Smoking Cessation
Cigarette smoking increases the risk of atherosclerotic vascular diseases, including MI, stroke, and PAD, stroke by 2- to 4-fold, and smoking cessation is associated with reductions in adverse cardiovascular event rates in these domains. Interestingly, cigarette smoking may also increase the risk of diabetes mellitus. In the Physician’s Health Study, smoking increased the risk 2-fold, and there was a dose response to pack-years smoked. Moreover, there may be a synergistic effect of cigarette smoking and insulin resistance in the development of atherosclerosis, suggesting a particularly important role in patients with diabetes mellitus. Smoking cessation interventions should be pursued aggressively, for the benefits in patients with diabetes mellitus at least match those found in patients without diabetes mellitus.

A variety of smoking cessation interventions are available, including counseling, nicotine replacement therapy, antidepressants (bupropion), and the nicotine partial receptor agonist, varenicline. There is no evidence for a treatment strategy of particular effectiveness in patients with diabetes mellitus.

Venous Thromboembolism
Diabetes mellitus may increase the risk of venous thromboembolism (VTE) via its effect on platelets and the components of the coagulation cascade. In a retrospective study of >700,000 Veterans Affairs patients, using International Classification of Diseases-9 codes to identify diabetes mellitus, the risk of pulmonary embolism was 27% higher in the diabetic patients. In a retrospective study of all patients admitted to a hospital with a venous thromboembolic event over a 2-year period, the age-adjusted risk for patients with type 1 or 2 diabetes mellitus was >2-fold that of patients without diabetes mellitus. In a population study of Olmstead county, however, diabetes mellitus did not increase the rate of VTE over a 25-year period.

One factor that may explain the variance is patient age. Data from the National Hospital Discharge Survey obtained over a 26-year period and including >92 million patients with diabetes mellitus showed an increased risk, but only in those <59 years of age. A nationwide Danish hospital study found that diabetes mellitus increased VTE risk in patients <55 years of age. Diabetes mellitus was reported to augment the risk of recurrent VTE in younger patients in the Worcester Venous Thromboembolism Study of 2488 consecutive patients with validated VTE. In a meta-analysis of >803 million participants, including 10.5 million patients with VTE, diabetes mellitus increased the risk of first VTE by 35% and first and recurrent events by 50%.

Conclusions
Both types 1 and 2 diabetes mellitus increase the risk of microvascular disease, atherosclerotic cardiovascular disease,
and likely, VTE. Within each of these conditions, the worse the underlying diabetes mellitus, as determined by disease duration, worse glycemic control, or requirement for insulin therapy, the more likely that vascular condition will progress or be associated with worse outcomes. Medical therapies, including blood pressure control, treatment of hyperglycemia, ACEIs, statins, and antplatelet therapies, reduce the risk of microvascular and macrovascular complications. Although the cardiovascular event rates have been declining over the last 2 decades, the incidence remains higher for patients with diabetes mellitus compared with nondiabetic patients. The increased prevalence of diabetes mellitus worldwide mandates the need for aggressive surveillance for the disease, and when detected, the institution of risk-reduction therapies. Understanding the pathophysiology of diabetes mellitus and its vascular complications as described in this compendium will foster new treatments to prevent and treat vascular disease in diabetes mellitus.

Disclosures
Dr Beckman report consultant from Astra Zeneca, Bristol Myers Squibb, Merck, Novartis and ownership of Janacare. The other author reports no conflicts.

References


64. Park SJ, Ahn JM, Kim YH, et al; BEST Trial Investigators. Trial of evero-


118. Randomised trial of a perindopril-based blood-pressure-lowering regi-

119. Torp-Pedersen C, Kaber L, Carlsten J. Angiotensin-converting enzyme inhibi-
tor after myocardial infarction: the Trandolapril Cardiovascular Education


124. Yusuf S, Diener HC, Sacco RL, et al; PRofESS Study Group. Telmisartan to pre-

125. NAVIGATe Study Group; McMurray JJ, Holman RR, Haffner SM, et al. Effect of valsartan on the incidence of diabetes and cardio-


126. McMurray JJ, Packer M, Desai AS, Gong J, LeFkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. PARADIGM-

HF Investigators and Committees. Angiotensin-neprilysin inhibition ver-

127. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk indi-


6736(04)61695-5.


131. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgerirsson G. Cholesterol lowering with simvastatin improves prog-

nosis of diabetic patients with coronary heart disease. A subgroup analy-


133. Wanner C, Krane V, Müll W, Olschewski M, Mann JF, Riz G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in


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