Diabetes and Vascular Disease
Pathophysiology, Clinical Consequences, and Medical Therapy: Part II

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In Part I, we addressed the pathobiology linking diabetes mellitus and atherosclerosis. Diabetes is a major risk factor for cardiovascular morbidity and mortality. This condition increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease up to 4-fold. Disease severity, as measured by chronic glycemia, is associated with an increasing frequency of clinical events in each vascular bed. The effect of diabetes on atherosclerosis is so pronounced that the benefit of female gender is eliminated in women with diabetes, who have an event rate similar to that of men with diabetes. Compared with patients without diabetes, those with diabetes have greater de novo disease progression and higher cardiovascular mortality rates. This part of the review will focus on clinical manifestations of and management strategies for atherosclerotic vascular disease in patients with diabetes.

Clinical Manifestations of Atherosclerosis in Diabetes

Coronary Artery Disease
Diabetes is associated with a 2- to 4-fold increase in the risk of developing coronary artery disease. The risk of a myocardial infarction in patients with diabetes and no evidence of coronary artery disease matches that of patients without diabetes who have had a previous myocardial infarction. In the recent report of the Adult Treatment Panel of the National Cholesterol Education Program, type 2 diabetes mellitus was accorded a coronary artery disease risk-equivalent. In patients with known coronary artery disease and diabetes, the rates of death approach 45% over 7 years and 75% over 10 years. Outcomes are worse in diabetic patients for each manifestation of coronary artery disease. Diabetic patients presenting with unstable angina are more likely to develop myocardial infarction, and diabetic patients with myocardial infarction are more likely to die than are nondiabetic individuals. In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry, a 6-nation unstable angina outcome study, diabetes increased mortality by 57%. The SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial of revascularization found a 36% increase in death in diabetic patients with cardiogenic shock complicating myocardial infarction. After myocardial infarction has occurred, the 1-month mortality rate is increased in diabetic patients by 58%. Approximately 50% of diabetic patients die 5 years after a myocardial infarction, double the rate found in nondiabetic patients.

Cerebrovascular Disease
Similarly, diabetes increases the risk of stroke. For example, the risk of stroke among patients taking hypoglycemic medications was increased 3-fold among the nearly 350,000 men in the Multiple Risk Factor Intervention Trial. In the Baltimore-Washington Cooperative Young Stroke Study, stroke risk increased more than 10-fold in diabetic patients younger than 44 years of age, ranging as high as 23-fold in young white men. Diabetes also increases stroke-related mortality, doubles the rate of recurrent stroke, and trebles the frequency of stroke-related dementia.

Peripheral Arterial Disease
Diabetes increases the incidence and severity of limb ischemia approximately 2- to 4-fold. Data from the Framingham cohort and Rotterdam studies show increased rates of absent pedal pulses, femoral bruits, and diminished ankle-brachial indices. Diabetic peripheral arterial disease often affects distal limb vessels, such as the tibial and peroneal arteries, limiting the potential for collateral vessel development and reducing options for revascularization. As such, patients with diabetes are more likely to develop symptomatic forms of the disease, such as intermittent claudication and critical limb ischemia, and undergo amputation. In the Framingham cohort, the presence of diabetes increased the frequency of intermittent claudication by more than 3-fold in men and women.
TABLE 1: Relationship Between Improved Glycemic Control and Risk of Cardiovascular Disease in Patients With Diabetes

| Trial                          | No. of Patients | Duration, y | Glycemic Control          | Outcome                                | Rate, % | Relative Risk |
|-------------------------------|-----------------|-------------|---------------------------|----------------------------------------|---------|---------------|
| Kuusisto, 1997                | 1059            | 7.2         | HbA1c ≥10.7% vs <10.7%    | CHD death                              | NA      | 1.4           |
| San Antonio Heart Study, 1998 | 4875            | 7.5         | FPG 8 to 11.5 mmol/L vs <8 mmol/L | CV death                               | 6.3 vs 2.8 | 2.9         |
| UKPDS, 1988                   | 3055            | 7.9         | HbA1c >7.5% vs <6.2%      | Fatal MI                               | NA      | 1.72          |

*Trial = Study No. of Patients Duration, y Glycemic Control Outcome Rate, % Relative Risk

HbA1c indicates glycosylated hemoglobin; FPG, fasting plasma glucose; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; and NA, not applicable.

Modified from Sowers JR, Haffner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. *Hypertension.* 2002;40:781–788.

more than 8-fold in women.4 Diabetes is the No. 1 cause of nontraumatic amputations in the United States. For patients aged 65 to 74 years, diabetes heightens the risk of amputation more than 20-fold, putting these patients at great risk for limb loss.26

**Medical Management of Atherosclerosis in Diabetes**

The diffuse nature and severity of atherosclerosis in patients with diabetes necessitates aggressive use of established therapies to minimize cardiovascular risk. Treatment should include correction of the metabolic disturbances and modification of related atherosclerotic risk factors, such as hypertension and dyslipidemia (Tables 1 through 3). Target-driven, intensive intervention directed at multiple risk factors reduces the risk of cardiovascular events, as well as microvascular events, by ~50% in patients with type 2 diabetes.27

**Treating Hyperglycemia and Insulin Resistance**

Glycemic control remains a principal intervention for prevention of microvascular disease, including retinopathy and nephropathy.28,29 Although the epidemiological link between elevations in glucose and the risk of cardiovascular disease is clear,30 the impact of glycemic control with the currently used drugs is modest at best. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that strict glycemic control (a hemoglobin A1c of 7% in the intervention group) did not decrease the risk of death, stroke, or amputation, and reached only a trend for myocardial infarction (P=0.052).29 The lack of benefit with glycemic control may have resulted from the small difference between the 2 groups (Δ hemoglobin A1c of 0.9%) or from inadequate glycemic control. Also, the target hemoglobin A1c of 7% in the intensive treatment group may not have been low enough to reduce the risk of myocardial infarction, which occurs with even modest elevations in blood glucose.30

Improvements in insulin sensitivity may have therapeutic promise. In the UKPDS, one arm of the study demonstrated that enhancing insulin sensitivity with the biguanide metformin decreased macrovascular events. Yet the addition of metformin to a sulfonylurea increased the risk of cardiovascular sequelae.29,31 The thiazolidinedione class of hypoglycemic drugs improves insulin sensitivity by binding the peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear receptor that participates in the regulation of adipose differentiation.32 PPAR-γ receptors are expressed in monocyte/macrophages of atherosclerotic lesions.33 Activation of PPAR-γ with troglitazone inhibits activity of matrix metalloproteinase-9 in human macrophages.33 Thiazolidinediones have been reported to improve endothelial function in patients with type 2 diabetes.34,35 Studies evaluating their role in diabetic atherosclerosis are ongoing.

**Hypertension**

In contrast to the management of hyperglycemia, several studies have found that aggressive management of hypertension decreases the risk of macrovascular disease and death in persons with diabetes. UKPDS was the first study to demonstrate the benefit of tight blood pressure control (systolic blood pressure of 144 versus 154 mm Hg over 9 years), evaluating a strategy of initial use of atenolol or captopril compared with placebo.36 The study demonstrated a significant decrease in the risk of stroke and death, with equal efficacy of the 2 agents. The majority of subjects required 2 or 3 drugs to control their blood pressure at the completion of follow-up.

More recently, the importance of the renin–angiotensin axis has come into focus. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers reduce the risk of progressive nephropathy in patients with type 1 and type 2 diabetes, respectively.37–40 In the Heart Outcomes and Prevention Evaluation, nonhypertensive diabetic subjects with an additional risk factor for vascular disease or with clinically evident vascular disease were treated with ramipril or placebo. The ramipril-treated group had a modest drop in blood pressure and a significant decrease in myocardial infarction, stroke, and death.41 Ramipril treatment also was associated with a 34% reduction in new-onset diabetes.42 The mechanism whereby ACE inhibitors improve glucose metabolism and protect against the development of clinical diabetes is not known. ACE inhibitors may limit cross-talk between angiotensin II and insulin, thereby interfering with the effects of angiotensin II on insulin signaling.42 Also, ACE inhibitors may improve blood flow and insulin delivery to metabolically active tissues, resulting in more effective glucose metabolism. Antagonism of the renin–angiotensin axis is particularly important in hypertensive diabetic patients. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, diabetic patients were randomized to losartan or atenolol, with hydrochlorothiazide as the second agent in both groups. Despite equivalent blood pressure lowering, losartan reduced the combined end point of cardiovascular death, stroke, or myocardial infarction by 24%; total mortality by 39%; and the rate of new onset of diabetes by 25% compared with atenolol.43,44
Dyslipidemia

Patients with type 2 diabetes are likely to have dyslipidemia characterized by elevated triglycerides and low HDL cholesterol. Large clinical trials have demonstrated the benefit of lipid-lowering therapy in diabetes. The drug class with the most impressive data in diabetic patients is that of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins. Retrospective analyses of the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events (CARE) trial have demonstrated that statin therapy reduced the risk of cardiovascular events in diabetic patients with coronary artery disease and elevated or average LDL cholesterol by 55% and 24%, respectively.45,46 Recently, the Heart Protection Study (HPS) prospectively randomized patients between the ages of 40 and 80 years with diabetes and/or vascular disease and total cholesterol $>135$ mg/dL to simvastatin or placebo.47 Among the nearly 3000 diabetic subjects without evidence of atherosclerosis at entry, there was a 34% risk

| Trial        | No. of Patients | Duration, y | Blood Pressure Control | Initial Therapy | Outcome                                      | Risk Reduction, % |
|--------------|-----------------|-------------|------------------------|-----------------|----------------------------------------------|-------------------|
| SHEP, 1996   | 583             | 5           | 155/72*                | Chlorthalidone  | Stroke                                       | NS                |
| Syst-Eur, 1999 | 492            | 2           | 162/82                 | Nitrendipine    | Stroke                                       | 69                |
| HOT, 1998    | 1501            | 3           | 144/85*                | Felodipine      | CV events                                    | 51                |
| UKPDS, 1999  | 1148            | 8.4         | 154/87                 | Captopril or atenol | Diabetes-related end points | 34                |
| HOPE, Micro-HOPE, 2000 | 3577 | 4.5 | Changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) | Ramipril vs placebo | CVD events | 25 |
| CAPP, 2001   | 572             | 7           | 155/89 vs 153/88       | Captopril vs diuretics or \(\beta\)-blockers | Fatal + NFMI + stroke + CV deaths | 41 |
| IDNT, 2001   | 1715            | 2.6         | 135/85                 | Irbesartan vs amlodipina or placebo | Doubling of serum creatinine + end-stage renal disease + death from any cause | 23 (vs amlodipina) |
| IRMA, 2001   | 590             | 2           | 144/83                 | Irbesartan 150 mg or 300 mg vs placebo | Onset of diabetic nephropathy | 20 (vs placebo) |
| RENAAL, 2001 | 1513            | 3.4         | 152/82 vs 153/82       | Losartan vs placebo in addition to conventional therapy | Doubling of serum creatinine | 25 |
| LIFE, 2002   | 1195            | 4.8         | 146/79 vs 148/79       | Losartan vs atenol | CV events | 22 |

SHEP indicates Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic hypertension in Europe; HOT, Hypertension Optimal Treatment; CAPP, Captopril Prevention Project; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA, IRbesartan Microalbuminuria in type 2 diabetes; RENAAL, Reduction in End points in NIDDM with Angiotensin II Antagonist Losartan; CVD, cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; NFMI, nonfatal myocardial infarction; and NS, not significant.

*Blood pressure in diabetic + nondiabetic population because blood pressure not reported for diabetic patients alone.

Data derived from Sowers JR, Haffner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension. 2002;40:781–788.
reduction in the combined end point of coronary heart disease, stroke, and revascularization over a 5-year follow-up period. Thus, in patients with type 2 diabetes above the age of 40 years, statin therapy is clearly beneficial and should be instituted.

The fact that reconstituted HDL improves endothelial function in hypercholesterolemia suggests that drugs capable of elevating the levels of these lipoproteins might be clinically beneficial. Niacin increases HDL cholesterol levels more than other available lipid therapies. Several trials have found that treatment of diabetic patients with niacin increases HDL cholesterol and reduces triglyceride levels without adversely affecting glucose control. The effect of niacin on cardiovascular outcomes in patients with diabetes is not known, and it should be considered a second-line agent to be used with caution because of a variety of adverse effects including flushing, hyperuricemia, hyperglycemia, and hepatic dysfunction.

Fibric acid derivatives represent the other major class of lipid modification therapy in diabetes. As PPAR-α agonists, these medications raise HDL and lower triglyceride levels. In the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), patients with a history of coronary artery disease, normal LDL levels, and low HDL levels were randomized to gemfibrozil or placebo. Over a 5.1-year follow-up period, there was a 24% reduction in death from coronary heart disease, nonfatal myocardial infarction, and stroke in the diabetic and nondiabetic patients. Fibric acid derivatives can be useful in the patient with persistently elevated triglyceride and low HDL levels, despite tight regulation of glycemia. There is a risk of myositis with the joint use of statins and fibric acid derivatives, so this combination requires careful monitoring.

**β-Adrenergic Blockers**

The fear of masking the symptoms of hypoglycemia has limited the use of β-adrenergic blockers in patients with diabetes. Yet β-blockers decrease the rate of events more in diabetic subjects than in patients without diabetes. In a retrospective study of 45 000 patients admitted to the hospital with a myocardial infarction, β-blockers reduced the rate of death at 1 year by 23% in patients with type 2 diabetes, compared with 13% in nondiabetic patients. There was no significant effect on glycemia-related complications. Thus, β-adrenergic blockade should be used in patients with diabetes and known coronary artery disease.

**Antiplatelet Therapy**

Antiplatelet therapy should be implemented in patients with diabetes and atherosclerosis unless contraindicated. The Antiplatelet Trialists’ Collaboration analyzed the results of 195 trials of >135 000 patients at high risk of arterial disease and found that platelet antagonists lowered the risk of stroke, myocardial infarction, and vascular death. The Early Treatment Diabetic Retinopathy Study randomized 3711 patients with diabetes and generally no history of myocardial infarction or stroke to aspirin (650 mg daily) or placebo. The relative risk for fatal or nonfatal myocardial infarction among the aspirin-treated patients was 0.83 (99% confidence interval: 0.66 to 1.04), without increased risk for retinal or vitreous hemorrhage. In acute coronary syndromes, platelet antagonists may be more effective in diabetic than nondiabetic subjects. A meta-analysis of the diabetic population of 6 large-scale trials of intravenous platelet glycoprotein (Gp) IIb/IIIa inhibitors in the medical management of acute coronary syndromes demonstrated that these agents reduce mortality by ~25% at 30 days in diabetic patients but had no survival benefit in nondiabetic patients. In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, the addition of clopidogrel to aspirin led to a reduction in death, myocardial infarction, or stroke in patients with unstable angina/non–ST-segment-elevation myocardial infarction, irrespective of their diabetes status. In the aggregate, these findings underscore the importance of antiplatelet therapy in the short-term and long-term management of diabetic patients with atherosclerosis. It is also reasonable to consider antiplatelet therapy in diabetic patients who have not had clinical manifestations of atherosclerosis because platelet function is abnormal in patients with diabetes (as reviewed in Part I), and many have atherosclerosis that has not become clinically evident.
Revascularization Strategies in Diabetes
Patients with diabetes often have severe atherosclerosis and a greater likelihood of end-organ ischemia requiring revascularization. Strategies for revascularization must take into account the higher risk for restenosis and graft occlusion, as well as the comorbid sequelae that complicate interventions in diabetic patients.

Coronary Revascularization
Considerations with regard to percutaneous coronary intervention or coronary artery bypass surgery for diabetic patients evolve as advances in technology provide more effective means of performing revascularization. The risk of restenosis and adverse outcomes with percutaneous coronary interventions is worse in diabetic than in nondiabetic patients.61,62 The Bypass Angioplasty Revascularization Investigation (BARI) found that 5-year survival rate was better for diabetic patients treated with bypass surgery than for those undergoing percutaneous transluminal coronary angioplasty (PTCA).63 Stents were not included in BARI because the study took place before 1996. Restenosis rates are lower in patients with diabetes treated with stents compared with those treated with just PTCA.64 In the diabetic population included in the Arterial Revascularization Therapy Study (ARTS), 1-year event-free survival was lower in those treated with stents than in those treated with coronary artery bypass surgery.65 Much of the difference related to repeat revascularization procedures. The use of Gp IIb/IIIa inhibitors at the time of stent placement reduces the 6-month risk of death, myocardial infarction, and target vessel revascularization among diabetic patients.66,67 In one study, abciximab therapy significantly reduced the risk of myocardial infarction or death at 6 months in diabetic patients treated with stents or balloon angioplasty.67 In another prospective trial, periprocedural administration of the small-molecule tirofiban and the antibody fragment abciximab led to overall similar outcomes among diabetic subjects undergoing stent-based percutaneous coronary intervention.66 It remains to be determined whether rapamycin-eluting stents will improve outcome in diabetic patients undergoing percutaneous coronary interventions.

Peripheral Revascularization
Diabetic patients with progressively disabling claudication and those with critical limb ischemia should be considered for revascularization. Decisions about endovascular or open surgical procedures depend in large part on the severity and distribution of the arterial lesions.68 Outcomes of iliac artery percutaneous transluminal angioplasty (PTA) and stenting in patients with diabetes have been reported as similar or worse than those in nondiabetic patients.69–71 The long-term patency rates after femoral-popliteal PTA are lower in diabetic than in nondiabetic patients.70,72 The long-term patency rates of tibio-peroneal artery PTA are low in diabetic and nondiabetic patients but may be sufficient in the short term to facilitate healing of foot ulcers. Graft patency rates are similar in diabetic and nondiabetic patients after surgical revascularization; however, there is a greater rate of limb loss in diabetic patients with critical limb ischemia because of persistent foot infection and necrosis.73,74 Also, the risk of perioperative cardiovascular events is increased in patients with diabetes.75,76

Carotid Artery Revascularization
The indications for carotid artery revascularization are the same in diabetic and nondiabetic patients. The incidence of stroke is reduced in patients with significant carotid artery stenoses and symptoms of cerebrovascular ischemia who undergo endarterectomy.77,78 Surgery also may benefit patients with asymptomatic carotid artery stenoses.79 The presence of diabetes does not seem to increase the periprocedural risk of stroke.80,81 The effect of diabetes on the results of carotid stenting is not known.

Conclusion
Diabetes markedly increases the risk of coronary, cerebral, and peripheral atherosclerosis and the clinical consequences of myocardial infarction, stroke, limb ischemia, and death. Aggressive medical management directed at optimizing glucose control, achieving normal blood pressure, correcting dyslipidemia, and inhibiting platelet function reduces the likelihood of these adverse cardiovascular events. In patients with severe atherosclerosis, revascularization is often necessary to avert the risk of end-organ damage. The selection of percutaneous or open surgical procedures depends on many factors, including the specific clinical occurrence, comorbidities, circulatory region involved, and technical feasibility. Cardiovascular physicians should be aware of the important relationship between diabetes and atherosclerosis and be prepared to institute appropriate medical and interventional treatments to reduce disability and death in these patients.

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