CHAPTER 75
Peripheral vascular and cerebrovascular disease in diabetes mellitus

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Key points
• Diabetes is frequently associated with atherosclerotic vascular disease including coronary, peripheral, and cerebrovascular disease.
• Early diagnosis of PAD in diabetic patients is critically important for the prevention of progression of disease as well as for prediction and subsequent reduction of overall cardiovascular risk.
• The American Diabetes Association (ADA) consensus statement recommends that a screening ABI be performed in all diabetic individuals >50 years of age.
• Current evidence highlights the importance of adopting a multi-factorial approach for the prevention of vascular complications in patients with type 2 diabetes. Lowering of blood pressure with regimens based on a variety of antihypertensive drugs, including ACE inhibitors, ARBs, β-blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events in diabetics.
• Cardiovascular physicians should be aware of the strong association between diabetes and atherosclerosis and use appropriate medical and interventional treatments to reduce disability and death in these patients.

Introduction
Diabetes mellitus is an established risk factor for atherosclerosis, and the risk of atherosclerotic vascular disease and its major clinical consequences, which include coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease, is markedly increased among individuals with diabetes. The increased risk appears to be independent of, and additive to, other cardiovascular risk factors [1]. Epidemiologic studies suggest that atherosclerosis causes most of the morbidity and mortality in patients with diabetes, particularly in the burgeoning type 2 diabetic patient population [2]. The Verona Diabetes Study demonstrated that cardiovascular disease is responsible for 44% of all-cause mortality in the diabetic patient population [3]. The duration of diabetes increases the risk of death from cardiovascular disease, independent of coexisting risk factors. Insulin resistance and its attendant metabolic abnormalities appear to play a pivotal role in the pathophysiology of the increased cardiovascular risk of diabetes [4].

Diabetes and risk of vascular disease
A meta-analysis of individual records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease attempted to quantify the magnitude of associations of diabetes mellitus and fasting glucose concentration with risk of coronary heart disease and major stroke subtypes [5]. Analyses included data for 698,782 people (52,765 nonfatal or fatal vascular outcomes; 8.49 million person-years at risk) from 102 prospective studies. Adjusted HRs with diabetes were: 2.00 (95% CI 1.83–2.19) for coronary heart disease; 2.27 (1.95–2.65) for ischemic stroke; 2.27 (1.95–2.65) for ischemic stroke; 1.56 (1.19–2.05) for hemorrhagic stroke; 1.84 (1.59–2.13) for unclassified stroke; and 1.73 (1.51–1.98) for the aggregate of other vascular deaths. Overall, it appears that diabetes confers about a twofold excess risk for a wide range of vascular diseases, independent from other conventional risk factors [5]. In T2DM, both angiogenesis and microangiopathy are increased and may contribute to accelerated atherosclerosis and the development of vulnerable plaque [5]. Hyperglycemia is a driving force in both large- and small-vessel disease [6].

Diabetes and peripheral arterial disease
Peripheral arterial disease (PAD) affects approximately 12 million people in the US and approximately 20–30% of these
patients have diabetes [1]. In studies using the ankle–brachial index (ABI), the prevalence of PAD (defined as an ABI <0.90) in diabetic individuals ranges from 20% to 30% [7]. Overall, diabetes is associated with a two- to fourfold increase in the incidence of PAD and an abnormal ABI is present in ~15% of diabetes patients [2,8]. Both intermittent claudication and critical limb ischemia are increased in diabetes. The prevalence of PAD increases with advancing age, duration of diabetes, and other risk factors such as smoking, dyslipidemia, and hypertension. The degree of diabetic control is also an independent risk factor for PAD; with every 1% increase in glycosylated hemoglobin, the risk of PAD has been shown to increase by 28% [9]. Early diagnosis of PAD in diabetic patients is critically important for the prevention of progression of disease as well as for prediction and subsequent reduction of overall cardiovascular risk. The distribution of atherosclerosis differs in diabetics and nondiabetics with stenotic lesions in patients with diabetes often located more distally than in nondiabetic subjects. Thus, the typical diabetic PAD lesions are located in the popliteal artery or in the runoff vessels below the knee, that is, the anterior tibial, posterial tibial, and the peroneal arteries [10,11]. The involvement of the distal limb vessels, such as the tibial and peroneal arteries, limits the potential for collateral vessel development and reduces options for revascularization [10]. Another hallmark of diabetic PAD is the calcification of the media layer of the arterial wall which may confound some diagnostic tests, a highly characteristic feature of T2DM [12,13].

A patient with chronic ischemic rest pain, ulcers, and gangrene due to arterial disease. It is important to consider that ulcers may often exist in the diabetic foot despite a normal macrocirculation. These ulcers may be due to disease in the microcirculation or related to neuropathy or sometimes multifactorial due to combination of impaired circulation, neuropathy, and infection.

### Diagnosis

A thorough medical history and physical examination is indicated in evaluating a diabetic individual for the presence of PAD. Information about the onset and duration of symptoms, pain characteristics, and any alleviating factors is helpful. Symptoms of leg ischemia in diabetic patients with peripheral neuropathy may be atypical and may delay diagnosis. Rather than experiencing cramping pain in legs or typical claudication, the patient may suffer from leg fatigue or inability to walk at their normal speed. If the patient has typical claudication, the claudication distance should be recorded at each visit and a shortening claudication distance signals progression of disease. The clinical stage of symptomatic PAD can be classified using the Fontaine staging system (Table 75.1). Fontaine stage I represents asymptomatic PAD; stages IIa and IIb include patients with mild and moderate-to-severe intermittent claudication, respectively; those with ischemic rest pain are classified as Fontaine stage III; and patients with tissue breakdown in the form of distal ulceration and gangrene represent Fontaine stage IV. A typical history of claudication has a low sensitivity, but a high specificity for PAD in diabetic individuals [14].

A complete physical examination is very important for the diagnosis of PAD in these individuals. Palpation of pulses in the leg and visual inspection of the feet are essential. Dependent rubor, pallor when the foot is elevated, absence of hair growth, and dystrophic toenails are signs of peripheral ischemia. In addition to measurement of ABI, physical examination should include blood pressure measurement, palpation of peripheral pulses, and auscultation of pulses and bruits. Palpation of peripheral pulses should include an assessment of the femoral, popliteal, and pedal vessels and pulses graded as absent, diminished, or normal. Dorsalis pedis pulse abnormalities are less sensitive for PAD, since up to 30% of these abnormalities may be due to a congenital absence of the dorsalis pedis artery. The absence of both the dorsalis pedis pulse and the posterior tibial pulse strongly suggests the presence of PAD. Figure 75.1 shows a typical protocol for the diagnosis of PAD in patients with diabetes.

An objective measure of peripheral vascular disease is the ABI, defined as the ratio between the arterial pressure at the ankle level (dorsalis pedis or posterior tibial) and in the left or right brachial artery with the highest pressure. The ABI should normally be above 0.9. This measurement is valuable for early detection of PAD and also for a better stratification of the overall cardiovascular risk. An ABI below 0.5 is indicative of severely impaired circulation of the foot. An ABI >1.4 is also abnormal and indicates poorly compressible vessels as a result of stiff arterial walls, which usually in diabetic patients are due to atherosclerosis in the media layer of the arterial wall. In situations where an elevated ABI is recorded or a pseudonormal value is suspected, the blood pressure should also be measured at the level of the toe by a minicuff and a technique suitable for blood flow detection in the toe. This is called the toe–brachial index (TBI).

The American Diabetes Association (ADA) consensus statement recommends that a screening ABI be performed in all diabetic individuals >50 years of age [1]. If normal (0.91–1.40), the test should be repeated every 5 years. An ABI should also be performed in any patient with symptoms suggestive of PAD. It should be recognized that ABI determinations may be of limited value in some patients with diabetes, because calcification of the tibial arteries may render them noncompressible, resulting in unusually high ABI values (>1.40). Under these conditions, the ABI cannot distinguish patients who have arterial occlusion from those who do not, making the ABI unhelpful. As a result,

### Table 75.1 Fontaine classification of peripheral arterial disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>IIa</td>
<td>Mild claudication (&gt;200 M)</td>
</tr>
<tr>
<td>IIb</td>
<td>Moderate to severe claudication (≤200 M)</td>
</tr>
<tr>
<td>III</td>
<td>Ischemic rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Tissue loss or ulceration</td>
</tr>
</tbody>
</table>
Peripheral vascular and cerebrovascular disease in diabetes mellitus

1.40 ≤ 0.90

ABI

PAD

Evaluate other causes of leg symptoms

Vascular laboratory

PVR; toe pressure measurement; UDS

Patient history and physical examination

Age 50–69 years and smoking or diabetes

Leg symptoms with exertion or reduced physical functioning

Abnormal leg vascular examination

Assessment of cardiovascular risk

> 1.40

0.91–1.40

≤ 0.90

Claudication symptoms

ABI treadmill test

Normal post-exercise ABI

Decreased post-exercise ABI

Figure 75.1 Typical protocol for the diagnosis of peripheral arterial disease in patients with diabetes. Source: Hiatt 2001 [14]. Reproduced with permission of Massachusetts Medical Society.

measurement of great toe artery pressure for calculation of TBI is commonly advocated in diabetic patients. Studies have suggested that assessment of TBI is the method of choice in the presence of overt calcification as defined by an ABI of >1.4 [15,16]. However, an elevated ABI is still predictive of an increased risk of cardiovascular events, and other noninvasive vascular tests should be considered to make the diagnosis of PAD. Transcutaneous oxygen (TcPO₂) measurement is another useful noninvasive modality that can prospectively determine severity of foot ischemia, and aid in selecting appropriate treatment for patients with diabetes and foot salvage problems [17].

In the patient with PAD in whom further investigation is required, for example in planning a revascularization procedure, the next step would be evaluation for segmental pressure and pulse volume recordings. Both tests aid in the localization of arterial occlusive lesions. Other noninvasive imaging techniques, such as ultrasonic duplex scanning or magnetic resonance angiography (MRA), can be used when more precise measurements of the morphological features of occlusions are required for planning revascularization options.

Ultrasound duplex scanning can directly visualize vessels, providing information on artery wall thickness, degree of flow turbulence, and changes in blood flow velocity which can be used to define severity of arterial stenosis [18]. Comprehensive imaging of the peripheral vasculature has traditionally been performed with invasive digital subtraction angiography. However, with the introduction of MRA and computed tomographic angiography (CTA), noninvasive imaging is now becoming a reality. Contrast-enhanced MRA produces images that are fairly comparable with conventional angiography. Recently, the resolution of CTA has dramatically improved image quality and expanded the applications for noninvasive angiography. At this point, CTA is replacing conventional angiography in some centers. Table 75.2 depicts the different methods for evaluating the peripheral circulation.

Treatment

One aim of medical management of PAD among diabetics is to aggressively modify cardiovascular risk factors to reduce the risk of future cardiovascular events (Table 75.3). It is also important
Table 75.2 Investigations of the peripheral circulation in diabetic patients

| At the physician’s office in every patient | • Inspection |
| • Palpation |
| • Pulses (radial, brachial, femoral, popliteal, dorsalis pedis, posterior tibial) |
| • Absence of hair growth |
| • Dystrophic toenails |
| • Ulcers or gangrenes |
| • Pressure measurement |
| • Ankle and arm blood pressure |

At the vascular laboratory (when appropriate)
• Distal and/or segmental pressure measurements
• Oscillography
• Treadmill testing (with or without distal pressure after exercise)
• Duplex sonography
• For evaluation of the microcirculation
• Transcutaneous oxygen pressure
• Vital capillaroscopy

At the radiology department
• Magnetic resonance imaging
• Angiography

Source: Adapted from Ryden 2007 [80]. Reproduced with permission of Oxford University Press.

Table 75.3 Recommendations for treatment of diabetic patients with peripheral arterial disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk increase for PAD</th>
<th>Treatment goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2.5</td>
<td>Cessation</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.0</td>
<td>Glycosylated hemoglobin &lt;7%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4.0 (per 10 mg DL^{-1} increase)</td>
<td>Low-density lipoprotein &lt;100 mg DL^{-1} *4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5</td>
<td>Blood pressure &lt;130/80 mmHg</td>
</tr>
</tbody>
</table>

*Consider <70 mg DL^{-1}.

PAD, peripheral arterial disease.
Source: Adapted from Marso 2006 [1]. Reproduced with permission of Elsevier.

to relieve the symptoms of intermittent claudication in order to improve functional status and quality of life. Smoking cessation, normalization of lipid abnormalities, and optimization of glycemic control are the most important steps that contribute to the prevention of primary or secondary cardiovascular disease in these patients. Table 75.3 describes general recommendations for treatment of diabetic patients with PAD.

PAD patients with diabetes tend to have more severe symptoms and a worse prognosis than nondiabetic patients [10], and the ACC/AHA guidelines concur with the American Diabetes Association (ADA) recommendations and note that aggressive management of diabetes has been shown to reduce the risk of nephropathy, retinopathy, and other microvascular events [19]. Intensive glycemic control may also reduce the risk of cardiovascular events in patients with PAD and diabetes, although there is a lack of clinical data specific to this population [19].

The Steno-2 study showed that the risk of both cardiovascular and microvascular complications was significantly reduced by about 50% in type 2 diabetic patients who received targeted, multifactorial management of glycemia, dyslipidemia, hypertension and microalbuminuria via lifestyle modification, pharmacologic therapy and secondary prevention with antiplatelet therapy, compared with patients conventionally managed according to national guideline recommendations [20]. Analysis of the Diabetes Control and Complications Trial, in which 1441 patients with T1DM were randomized to intensive or conventional treatment, showed that the risk of major peripheral vascular events in the group receiving intensive therapy was 22% lower than that in the conventional therapy group (0.43 vs. 0.55 events per 100 patient-years). This difference, however, was not statistically significant [21].

Glycemia
The UKPDS 33 study of 3867 newly diagnosed patients with T2DM showed that intensive antidiabetic treatment reduced the risk of complications by 12% (95% CI 1–21; p = 0.029) compared with conventional therapy [22]. Although this was primarily due to a reduction in microvascular complications, there was also a 16% reduction in MI (p = 0.052) with intensive treatment. The UKPDS long-term trials indicate that in patients with T2DM, intensive glucose control may have a legacy effect, whereas the same benefit may not apply to tight blood pressure control [23]. The studies highlight the importance of adopting a multifactorial approach for the prevention of vascular complications in patients with T2DM and reinforce the importance of maintaining good glycemic control, not only for the prevention of the renal and metabolic complications of diabetes but also for protection against the development of major cardiovascular disease in the long term [23]. A recent study, the Veterans Affairs Diabetes Trial (VADT) suggested that intensive glucose control in patients with poorly controlled T2DM had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria [24]. The study randomly assigned 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to therapy for T2DM to receive either intensive or standard glucose control. The median follow-up was 5.6 years. Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (hazard ratio (HR) in the intensive-therapy group, 0.88; 95% CI 0.74–1.05; p = 0.14). There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause (HR 1.07; 95% CI 0.81–1.42; p = 0.62) [24]. The Action to Control Cardiovascular Risk in
Diabetes (ACCORD) trial, which involved 10,251 patients with T2DM, attempted to determine whether intensive insulin therapy was associated with a lower incidence of cardiovascular events than standard therapy [25]. The study was specifically designed to address whether an HbA1c goal of <6%, to be attained by intensive therapy, would reduce cardiovascular events in patients with established cardiovascular disease or cardiovascular risk factors, as compared to a standard strategy using an HbA1c target of 7.0 – 7.9%. At a mean treatment duration of 3.5 years, the study was stopped prematurely on the recommendation of the Data and Safety Monitoring Board, owing to an increase in all-cause mortality in the intensive-therapy group compared with the standard-therapy group (5% vs. 4%; HR 1.22; 95% CI 1.01 – 1.46). The rate of death from cardiovascular causes was similarly increased in the intensive-therapy group (2.6% vs. 1.8%; HR 1.35; 95% CI 1.04 – 1.76). The primary outcome of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular cause was not significantly different in the group assigned to intensive glycemic control (6.9% vs. 7.2%; HR 0.90; 95% CI 0.78 – 1.04) [25]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial enrolled 11,140 patients with T2DM and pre-existing cardiovascular disease or at least one additional cardiovascular risk factor [26]. In contrast to the ACCORD trial, the primary outcome in the ADVANCE trial was a composite of microvascular events (nephropathy and retinopathy) and macrovascular disease defined by major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death). Intensive therapy was associated with a decrease in the incidence of the primary endpoint (a combination of microvascular and macrovascular events, as outlined earlier; 18.1% vs. 20.0%; HR 0.90; 95% CI 0.82 – 0.98) and of major microvascular events (9.4% vs. 10.9%; HR 0.86; 95% CI 0.77 – 0.97), compared with standard therapy. This benefit was primarily the result of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; HR 0.79; 95% CI 0.66 – 0.93), as intensive therapy had no statistically significant effect on the incidence of retinopathy or macrovascular events [26].

Despite the need for further study on the association of glycemic control and cardiovascular risk in patients with PAD and diabetes, both the ACC/AHA and the ADA recommend the reduction of HbA1c to <7.0% for this population [19,27,28]. The results from ACCORD, ADVANCE, and VADT should not be interpreted to abandon the general goal of <7% and diminish the importance of glycemic control. The lower-than-anticipated event rates observed in both intensive and standard treatment groups in these studies rather support the premise that a multifactorial approach should be used to address the major cardiovascular risk factors including regular physical activity, lipid lowering, blood pressure control, and so on.

**Antiplatelet therapy**

The use of antiplatelet agents is known to reduce future secondary cardiovascular events in patients with both diabetes mellitus and cardiovascular disease [29]. One study examined whether aspirin and antioxidant therapy, combined or alone, are more effective than placebo in reducing the development of cardiovascular events in patients with diabetes mellitus and asymptomatic PAD. A total of 1276 adults aged 40 or more with T1 or T2DM and an ankle–brachial pressure index of 0.99 or less but no symptomatic cardiovascular disease were enrolled [30]. Daily, 100 mg aspirin tablet plus antioxidant capsule (n = 320), aspirin tablet plus placebo capsule (n = 318), placebo tablet plus antioxidant capsule (n = 320), or placebo tablet plus placebo capsule (n = 318). Overall, 116 of 638 primary events occurred in the aspirin groups compared with 117 of 638 in the no aspirin groups (18.2% vs. 18.3%) (HR 0.98; 95% CI 0.76 – 1.26) [30]. This trial did not provide evidence to support the use of aspirin in primary prevention of cardiovascular events and mortality in the population with diabetes. Based on this and other available evidence, the American Diabetes Association suggests that low-dose (75 – 162 mg d<sup>−1</sup>) aspirin use for prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased risk for cardiovascular disease (10-year risk of CVD events >10%) and states that aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (men under age 50 years and women under 60 years with no major additional CVD risk factors [31]. The Antithrombotic Trialists’ (ATT) Collaboration performed a meta-analysis and suggested that in primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds [32].

**Lipids**

The Cholesterol Treatment Trialists’ (CTT) Collaborators analyzed data from 18,686 individuals with diabetes (1466 with type 1 and 17,220 with type 2) in the context of a further 71,370 without diabetes in 14 randomized trials of statin therapy [33]. During a mean follow-up of 4.3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol L<sup>−1</sup> reduction in LDL-cholesterol in participants with diabetes (rate ratio (RR) 0.91; 95% CI 0.82 – 1.01; p = 0.02), which was similar to the 13% reduction in those without diabetes (RR 0.87; 0.82 – 0.92; p < 0.0001). This finding reflected a significant reduction in vascular mortality (RR 0.87; 0.76 – 1.00; p = 0.008) and no effect on nonvascular mortality (RR 0.97; 0.82 – 1.16; p = 0.7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol L<sup>−1</sup> reduction in LDL-cholesterol in people with diabetes (RR 0.79; 0.72 – 0.86; p < 0.0001), which was similar to the effect observed in those without diabetes (RR 0.79; 0.76 – 0.82; p < 0.0001). In diabetic participants there were reductions in myocardial infarction or coronary death (RR 0.78; 0.69 – 0.87; p < 0.0001), coronary revascularization (RR 0.75; 0.64 – 0.88; p < 0.0001), and stroke (RR 0.79; 0.67 – 0.93; p = 0.0002). These findings would suggest that statin therapy be considered for all
diabetic individuals who are at sufficiently high risk of vascular events [33]. However, it should be noted that while statins are effective for cardiovascular disease prevention, they have recently been associated with an increased risk of new-onset diabetes mellitus [34,35]. Based on new data, the FDA changed statin labeling, incorporating the fact that there are studies showing that patients being treated with statins may have a small increased risk of increased blood sugar levels and of being diagnosed with T2DM. Based on totality of data, for the vast majority of patients who are on statins, the benefits are expected to outweigh the risks since statins are very effective at lowering risk for vascular disease and stroke. The justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial investigated whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events in apparently healthy men and women with LDL-cholesterol levels of less than 130 mg dL\(^{-1}\) (3.4 mmol L\(^{-1}\)) and high-sensitivity C-reactive protein levels of 2.0 mg L\(^{-1}\) or higher [36]. The study reported that rosuvastatin significantly reduced the incidence of major cardiovascular events [36]. The concern about new-onset diabetes should lead to open discussion between physician and patient and the risk–benefit assessed for each individual patient. It should also lead to increased vigilance about testing for diabetes in patients who are on statins.

Fibrates, introduced more than 35 years ago, based on favorable changes in the lipid profile, continue to generate controversy regarding their clinical efficacy. Two randomized, placebo-controlled trials of gemfibrozil had demonstrated improvements in cardiovascular outcomes but subsequent trials of bezafibrate and fenofibrate showed no significant overall cardiovascular benefit over placebo [37]. Based on contemporary evidence, it would appear that the benefit of adding a fibrate to statin therapy in reducing the risk of cardiovascular events in patients with T2DM is unproven. At this time, clinicians who choose to prescribe combination therapy should selectively target high-risk patients only after optimal control of LDL-cholesterol has been achieved with statin therapy [37].

**Blood pressure**

Hypertension is a common comorbidity of diabetes, affecting a significant proportion of patients, with prevalence depending on type of diabetes, age, obesity, and ethnicity. In T1DM, hypertension is often the result of underlying nephropathy, while in T2DM it usually coexists with other cardiometabolic risk factors. Epidemiologic analyses show that high blood pressure is associated with increased cardiovascular event rates and mortality in individuals with diabetes. Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to <140 mmHg systolic and <80 mmHg diastolic in individuals with diabetes but the evidence for benefits from lower systolic blood pressure targets is limited [38]. The current guidelines recommend that people with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and diastolic blood pressure <80 mmHg [38]. Lowering of blood pressure with regimens based on a variety of antihypertensive drugs, including ACE inhibitors, ARBs, \(\beta\)-blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events in diabetics. Although evidence for distinct advantages of RAS inhibitors on cardiovascular disease outcomes in diabetes remains conflicting, the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may favor using them as first-line hypertension therapy in people with diabetes [38].

**Lifestyle**

To relieve the symptoms of intermittent claudication, patients should exercise regularly. A regular walking regimen is extremely helpful. The best program is a stop-start walking regimen and includes regular daily walks, 30–45 min d\(^{-1}\), at least three times per week, for at least 6 months. Individuals should walk as far as possible using near maximal pain as a signal to stop and resume walking when pain goes away. A typical supervised exercise program is 60 min in duration and is monitored by a skilled nurse or technician. Patients may be encouraged to walk primarily on a treadmill since this most closely reproduces walking in the community setting. The initial workload of the treadmill is set to a speed and grade that bring on claudication pain within 3–5 min. Patients walk at this work rate until they achieve claudication of moderate severity. They then rest until the claudication abates, and then resume exercise. This repeated on-and-off form of exercise is continued throughout the supervised rehabilitation setting. On a weekly basis, patients should be reassessed clinically as they are able to walk further and further at their chosen workload. This then will necessitate an increase in speed or grade or both to allow patients to successfully work at harder and harder workloads [39–41]. Currently, two pharmacologic agents are approved for the symptomatic treatment of intermittent claudication: namely pentoxifylline and cilostazol. Pentoxifylline, a hemorheologic agent, decreases blood viscosity and improves erythrocyte flexibility [42]. The results of clinical trials demonstrating the efficacy of pentoxifylline in improving treadmill-walking distance have been equivocal, and there are insufficient data to justify generalized use in PAD [43]. Cilostazol, a phosphodiesterase inhibitor, is the most effective agent available in the US. Cilostazol (100 mg twice daily) has been shown to improve maximal walking distance by 40–50% compared with placebo [44,45]. In a direct comparison, the mean maximal walking distance in PAD patients treated with cilostazol for 24 weeks was significantly greater compared with that of patients who received pentoxifylline or placebo [46]. Because of concerns about the potential risk of mortality, cilostazol is contraindicated if any degree of systolic or diastolic heart failure is present or in patients with left ventricular systolic dysfunction [40].

Lifestyle
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 [47]. Outcomes of iliac artery percutaneous transluminal angioplasty (PTA) and stenting in patients with diabetes have been reported as similar to or worse than those in nondiabetic patients [48,49]. With respect to surgery, the long-term patency rates after femoral-popliteal PTA are also lower in diabetic than in nondiabetic patients [50]. The modality of revascularization among diabetic patients with PAD should be tailored to the clinical circumstance, lesion characteristics, and patient preference. In the future, dedicated trials directly comparing endovascular versus surgical revascularization in diabetic patients with PAD may help define optimal treatment. It is important that patients undergoing either percutaneous or surgical revascularization receive optimal secondary preventative therapy post procedure with antiplatelet and lipid-lowering agents.

Diabetes and cerebrovascular disease
The risk of stroke and transient ischemic attacks (TIA) is significantly increased in patients with diabetes [51–54]. In fact, cerebrovascular disease is the most common long-term cause of morbidity and mortality in patients with both T1 and T2DM. Since initial observations by the Framingham investigators, several large population-based studies have confirmed an increased frequency of stroke in the diabetic population [54,55]. Diabetes was the strongest single risk factor for stroke (relative risk for men 3.4 and for women 4.9) in a prospective study from Finland with a follow-up of 15 years [56]. Among stroke subtypes, diabetes is a prominent risk factor for ischemic stroke, but data on hemorrhagic stroke have been conflicting, One study suggested that the risk of stroke among patients taking hypoglycemic medications was increased threefold among the nearly 350,000 men in the Multiple Risk Factor Intervention Trial [57]. 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 [58]. Diabetes also increases stroke-related mortality, doubles the rate of recurrent stroke, and triples the frequency of stroke-related dementia [59,60].

Diabetes may also cause microatheromas in small vessels, such as the lenticulostrate arteries, leading to lacunar stroke, a common subtype of ischemic stroke. Lacunar stroke is a unique subtype and requires specific clinical and imaging features for diagnosis. Stroke patients with diabetes, or with hyperglycemia in the acute stage of stroke, have a higher mortality, worse neurologic outcome, and more severe disability than those without [61].

There is less information concerning the risk of stroke in T1 than in T2DM. The World Health Organization Multinational Study of Vascular Disease in Diabetes reported increased cerebrovascular mortality in type 1 diabetic patients however, with considerable variations between countries [62]. The data from the nationwide cohort of more than 5000 Finnish childhood-onset type 1 diabetic patients showed that, by the age of 50 years, the risk for an acute stroke was equal to that of an acute coronary event without any gender-related differences [63]. Presence of diabetic nephropathy was the strongest predictor of stroke, causing a 10-fold increase of risk. After correction for other risk factors for stroke, which are also more common in diabetic subjects, the risk still remained increased more than twofold meaning that diabetes itself is a strong independent risk factor for stroke [64].

Prevention of stroke
Measures to prevent stroke in diabetes should include a multipronged strategy targeted at treatment of hypertension, hyperlipidemia, microalbuminuria, hyperglycemia, smoking cessation, and the appropriate use of antiplatelet medication (Table 75.4).

Blood pressure
Results from the HOPE Study and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) suggest that the reduction of stroke incidence in diabetic subjects during treatment based on ACE-inhibitors was greater than would be anticipated from the blood pressure-lowering effect alone and the effect was also evident in normotensive individuals [65,66]. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study the same trend was found with an angiotensin receptor blocker, losartan [67]. However, in several other trials, including the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), there was no apparent benefit of one class of antihypertensive drug over another in this respect [68]. Current data suggests that optimal blood pressure lowering may be more important than a particular agent.

Lipids
Treatment with statins has been shown to reduce the incidence of stroke in high-risk patients, but the diabetic subpopulations in the trials have been too small to allow a reliable subgroup analysis. In the Heart Protection Study, a sizeable subgroup of 5963 diabetic patients was randomized to placebo or 40 mg of simvastatin daily. Simvastatin reduced the incidence of stroke by a robust 24% [69].

Antiplatelet therapy
Antiplatelet therapy has also been shown to reduce the incidence of stroke in diabetic patients and is indicated for both primary and secondary prevention of stroke [70]. Aspirin in a
### Table 75.4 Recommendations for prevention and treatment of stroke in diabetic patients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalization of blood pressure is recommended in all patients with diabetes for the prevention of stroke</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>For stroke prevention, blood pressure lowering is more important than the choice of drug</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Inhibition of the renin-angiotensin-aldosterone system may have additional benefits beyond blood pressure lowering per se</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Inhibition of the renin-angiotensin-aldosterone system may be considered also in diabetic patients with normal blood pressure levels</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Patients with stroke should be treated with statins according to the same principles as nondiabetic subjects with stroke</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Antiplatelet therapy with aspirin is recommended for primary and secondary prevention of stroke</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Patients with acute stroke and diabetes should be treated according to the same principles as stroke patients without diabetes</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Optimization of metabolic conditions including glycemic control should be aimed for</td>
<td>Ila</td>
<td>C</td>
</tr>
</tbody>
</table>

*a Class of recommendation.  
*b Level of evidence.

Source: Adapted from Ryden 2007 [80]. Reproduced with permission of Oxford University Press.

Low dose (75–325 mg daily) should be the drug of initial choice. In patients with recurrent stroke, a combination of aspirin and dipyridamole may be considered [71]. The alternative combination with aspirin and clopidogrel seems less safe since it was associated with an increased risk of bleeding without any benefit in terms of cardiovascular outcome in the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) Trial, performed in 7599 patients of whom 68% had diabetes [72]. In patients with atrial fibrillation, anticoagulant therapy should be given for stroke prevention.

#### Revascularization

The high frequency of early stroke following TIA mandates a workup within 7 days of the index event to reduce the risk of a subsequent, and potentially more serious, and even fatal neurologic event. Initial evaluation with echocardiography and carotid ultrasound is usually indicated. After a TIA or stroke caused by carotid-artery disease, medical treatments can be optimized in high-risk patients, avoiding the need for emergency carotid surgery thus allowing patients to undergo safer elective surgery [73]. Carotid endarterectomy for the prevention of stroke in patients with high-grade stenosis of the carotid artery has been shown to be effective, although it has not been specifically investigated in diabetic patients. Since complications during and after this procedure are more frequent in diabetic as compared with nondiabetic subjects, special consideration should be given to the overall risk for peri- and postoperative morbidity and mortality when deciding on surgical interventions in the patient with diabetes [74]. The presence of diabetes, however, does not seem to increase the perioperative risk of stroke [75,76]. An alternative to endarterectomy, carotid artery angioplasty and stenting (CAS), which has been found to be at least not inferior to endarterectomy, may prove to be a preferable method in high-risk patients [77] but the effects of diabetes on carotid stenting have not been well studied.

#### Treatment of acute stroke

The treatment in the acute phase of stroke in diabetic patients should follow the same principles that govern the treatment of stroke in the general population. Available studies have not suggested any interaction of diabetes with treatment [78]. Thrombolysis is an effective treatment for ischemic stroke if instituted within 3 hours of symptom onset. It reduces mortality and disability from stroke but is associated with a risk of hemorrhage and its use and effects in diabetes require further evaluation in clinical studies. Conservative treatment of stroke includes close surveillance of vital signs, optimization of circulation and metabolic conditions, including glycemic control, in a designated stroke unit. Patients should receive early neurologic rehabilitation with physical and occupational therapy to improve quality of life. Recent studies suggest that early intervention for hypertension during the acute phase of stroke may be beneficial but currently it is recommended to acutely reduce only very high blood pressures, above 220 mmHg systolic and/or 120 mmHg diastolic, and not lower blood pressure to levels that may enhance ischemia. Blood pressure should also not be lowered by more than 25% during the first day of treatment [79].
Conclusions

Noncoronary atherosclerotic disease such as PAD and cerebrovascular disease is a common finding in patients with diabetes. The risk of developing PAD and cerebrovascular disease is not only higher in patients with diabetes, but the disease is more severe and progresses aggressively than in nondiabetic individuals. In fact, diabetes is the most common cause of non-traumatic amputations in the United States. The major concern to patients with diabetes and PAD or cerebrovascular disease is from cardiovascular events, and the primary therapeutic goal is to modify and optimally treat atherosclerotic risk factors. Risk factor management in these individuals includes lifestyle modifications, treating associated conditions such as dyslipidemia and hypertension, and preventing ischemic events with antiplatelet therapy [81]. Pharmacologic therapies to improve symptomatic PAD include cilostazol and pentoxiphylline. A supervised exercise program should be the initial treatment step for the management of symptomatic PAD prior to starting pharmacologic therapy. Revascularization has an important role to play in the management of patients with both PAD and cerebrovascular disease for whom risk factor modification and pharmacologic treatment prove inadequate. Cardiovascular physicians should be aware of the strong association between diabetes and atherosclerosis and use appropriate medical and interventional treatments to reduce disability and death in these patients. Dedicated prospective studies are indicated to define optimal antiplatelet therapy and revascularization modality in diabetic patients.

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