Peripheral Arterial Disease in People With Diabetes

AMERICAN DIABETES ASSOCIATION

Peripheral arterial disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities. While PAD is a major risk factor for lower-extremity amputation, it is also accompanied by a high likelihood for symptomatic cardiovascular and cerebrovascular disease. Although much is known regarding PAD in the general population, the assessment and management of PAD in those with diabetes is less clear and poses some special issues. At present, there are no established guidelines regarding the care of patients with both diabetes and PAD.

On the 7–8 of May 2003, a Consensus Development Conference was held to review the current knowledge regarding PAD in diabetes. After a series of lectures by experts in the field of endocrinology, cardiology, vascular surgery, orthopedic surgery, podiatry, and nursing, a vascular medicine panel was asked to answer the following questions:

1) What is the epidemiology and impact of PAD in people with diabetes?

2) Is the biology of PAD different in people with diabetes?

3) How is PAD in diabetes best diagnosed and evaluated?

4) What are the appropriate treatments for PAD in people with diabetes?

1) WHAT IS THE EPIDEMIOLOGY AND IMPACT OF PERIPHERAL ARTERIAL DISEASE IN PEOPLE WITH DIABETES?

PAD is a manifestation of atherosclerosis characterized by atherosclerotic occlusive disease of the lower extremities and is a marker for atherothrombotic disease in other vascular beds. PAD affects ~12 million people in the U.S.; it is uncertain how many of those have diabetes. Data from the Framingham Heart Study (1) revealed that 20% of symptomatic patients with PAD had diabetes, but this probably greatly underestimates the prevalence, given that many more people with PAD are asymptomatic rather than symptomatic. As well, it has been reported that of those with PAD, over one-half are asymptomatic or have atypical symptoms, about one-third have claudication, and the remainder have more severe forms of the disease (2).

The most common symptom of PAD is intermittent claudication, defined as pain, cramping, or aching in the calves, thighs, or buttocks that appears reproducibly with walking exercise and is relieved by rest. More extreme presentations of PAD include rest pain, tissue loss, or gangrene; these limb-threatening manifestations of PAD are collectively termed critical limb ischemia (CLI).

PAD is also a major risk factor for lower-extremity amputation, especially in patients with diabetes. Moreover, even for the asymptomatic patient, PAD is a marker for systemic vascular disease involving coronary, cerebral, and renal vessels, leading to an elevated risk of events, such as myocardial infarction (MI), stroke, and death.

Diabetes and smoking are the strongest risk factors for PAD. Other well-known risk factors are advanced age, hypertension, and hyperlipidemia (3).

Potential risk factors for PAD include elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B, lipoprotein(a), and plasma viscosity. An inverse relationship has been suggested between PAD and alcohol consumption.

In people with diabetes, the risk of PAD is increased by age, duration of diabetes, and presence of peripheral neuropathy. African Americans and Hispanics with diabetes have a higher prevalence of PAD than non-Hispanic whites, even after adjustment for other known risk factors and the excess prevalence of diabetes. It is important to note that diabetes is most strongly associated with femoral-popliteal and tibial (below the knee) PAD, whereas other risk factors (e.g., smoking and hypertension) are associated with more proximal disease in the aorto-iliofemoral vessels.

The true prevalence of PAD in people with diabetes has been difficult to determine, as most patients are asymptomatic, many do not report their symptoms, screening modalities have not been uniformly agreed upon, and pain perception may be blunted by the presence of peripheral neuropathy. For these reasons, a patient with diabetes and PAD may be more likely to present with an ischemic ulcer or gangrene than a patient without diabetes. While amputation has been used by some as a measure for PAD prevalence, medical care and local indications for amputation versus revascularization of the patient with critical limb ischemia widely vary. The nationwide age-adjusted amputation rate in diabetes is ~8/1,000 patient years with a prevalence of ~3%. However, regional patterns differ—there is nearly a

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Abbreviations: ABI, ankle-brachial index; CABG, coronary artery bypass graft; CAPRIE, Clopidogrel versus Aspirin in Patients At Risk of Ischemic Events; CLI, critical limb ischemia; CRP, C-reactive protein; eNOS, endothelial cell nitric oxide synthase; FDA, Food and Drug Administration; FFA, free fatty acid; MI, myocardial infarction; MRA, magnetic resonance angiogram; NF-κB, nuclear factor-κB; PAD, peripheral arterial disease; PAI-1, plasminogen activator inhibitor-1; PI, phosphatidylinositol; PKC, protein kinase C; PVR, pulse volume recording; RAGE, receptor for advanced glycation end products; UKPDS, U.K. Prospective Diabetes Study; VSMC, vascular smooth muscle cell.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ninefold variation of major amputations in people with diabetes across the U.S. Therefore, the incidence and prevalence of amputation may be an imprecise measure of PAD.

The reported prevalence of PAD is also affected by the methods by which the diagnosis is sought. Two commonly used tests are the absence of peripheral pulses and the presence of claudication. Both, however, suffer from insensitivity. A more accurate estimation of the prevalence of PAD in diabetes should rely upon a validated and reproducible test. Such a test is the ankle-brachial index (ABI), which involves measuring the systolic blood pressures in the ankles (dorsalis pedis and posterior tibial arteries) and arms (brachial artery) using a hand-held Doppler and then calculating a ratio. Simple to perform, it is a noninvasive, quantitative measurement of the patency of the lower extremity arterial system. Compared with an assessment of pulses or a medical history, the ABI has been found to be more accurate. It has been validated against angiographically confirmed disease and found to be 95% sensitive and almost 100% specific (4). There are some limitations, however, in using the ABI. Calcified, poorly compressible vessels in the elderly and some patients with diabetes may artificially elevate values. The ABI may also be falsely negative in symptomatic patients with moderate aortoiliac stenoses. These issues complicate the evaluation of an individual patient but are not prevalent enough to detract from the usefulness of the ABI as an effective test to screen for and to diagnose PAD in patients with diabetes. Using the ABI, one recent survey (5) found a prevalence of PAD in people with diabetes >40 years of age to be 20%, a prevalence greater than anticipated using less reliable measures, such as symptoms or absent pulses. Moreover, another survey of patients with diabetes >50 years of age showed a prevalence of PAD of 29% (6). Thus, the prevalence of PAD in diabetes appears higher than previously estimated.

Impact of PAD

The impact of PAD can be assessed by its progression, the presence of symptoms, and the excess cardiovascular events associated with systemic atherosclerosis. Approximately 27% of patients with PAD demonstrate progression of symptoms over a 5-year period, with limb loss occurring in ~4%. While the majority of patients remain stable in their lower-limb symptomatology, there is a striking excess cardiovascular event rate over the same 5-year time period, with 20% sustaining nonfatal events (MI and stroke) and a 30% mortality rate (7). For those with CLI, the outcomes are worse: 30% will have amputations and 20% will die within 6 months (8). The natural history of PAD in patients with diabetes has not specifically been studied longitudinally, but it is known from prospective clinical trials of risk interventions that the cardiovascular event rates in patients with PAD and diabetes are higher than those of their nondiabetic counterparts.

Diagnosis of PAD

Diagnosing PAD is of clinical importance for two reasons. The first is to identify a patient who has a high risk of subsequent MI or stroke regardless of whether symptoms of PAD are present. The second is to elicit and treat symptoms of PAD, which may be associated with functional disability and limb loss. PAD is often more subtle in its presentation in patients with diabetes than in those without diabetes. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in diabetic patients the lesions are more likely to be more diffuse and distal. Importantly, PAD in individuals with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback. Thus, a classic history of claudication may be less common. However, a patient may elicit more subtle symptoms, such as leg fatigue and slow walking velocity, and simply attribute it to getting older. It has been reported that patients with PAD and diabetes experience worse lower-extremity function than those with PAD alone (9). Also, diabetic patients who have been identified with PAD are more prone to the sudden ischemia of arterial thrombosis (10) or may have a pivotal event leading to neuroischemic ulceration or infection that rapidly results in an acute presentation with critical limb ischemia and risk of amputation. By identifying a patient with subclinical disease and instituting preventative measures, it may be possible to avoid acute, limb-threatening ischemia.

PAD in diabetes also adversely affects quality of life, contributing to long-term disability and functional impairment that is often severe. Patients with claudication have a slower walking speed (generally <2 mph) and a limited walking distance. This may result in a "cycle of disability" with progressive deconditioning and loss of function. Finally, there are significant economic costs of health care, reduced productivity, and personal expenses associated with a chronic manifestation of atherosclerotic disease such as PAD.

2) IS THE BIOLOGY OF PAD DIFFERENT IN PEOPLE WITH DIABETES?

Diabetes affects nearly every vascular bed; however, the pervasive influence of diabetes on the atherothrombotic milieu of the peripheral vasculature is unique. The abnormal metabolic state accompanying diabetes results in changes in the state of arterial structure and function. The onset of these changes may even predate the clinical diagnosis of diabetes. Relatively little is known about the biology of PAD in individuals with diabetes in particular. However, it is felt that the atherogenic changes observed with other manifestations of atherosclerotic disease, such as coronary and carotid artery disease, are generally applicable to patients with both PAD and diabetes.

The proatherogenic changes associated with diabetes include increases in vascular inflammation and derangements in the cellular components of the vasculature, as well as alterations in blood cells and hemostatic factors. These changes are associated with an increased risk for accelerated atherogenesis as well as poor outcomes. Given the large size of the peripheral vascular bed, the potential impact of these abnormalities is great.

Diabetes, inflammation, and risk for PAD

Inflammation has been established as both a risk marker and perhaps a risk factor for atherothrombotic disease states, including PAD (11). Elevated levels of CRP are strongly associated with the development of PAD (12). In addition, levels of CRP are abnormally elevated in patients with impaired glucose regulation syndromes, including impaired glucose tolerance and diabetes.

In addition to being a marker of disease presence, elevation of CRP may also be a culprit in the causation or exacerbation of PAD. CRP has been found to bind to endothelial cell receptors promoting apoptosis and has been shown to colocal-

ize with oxidized LDL in atherosclerotic plaques. CRP also stimulates endothelial production of procoagulant tissue factor, leukocyte adhesion molecules, and chemotactic substances and inhibits endothelial cell nitric oxide (NO) synthase (eNOS), resulting in abnormalities in the regulation of vascular tone. Finally, CRP may increase the local production of compounds impairing fibrinolysis, such as plasminogen activator inhibitor (PAI)-1.

Diabetes and endothelial cell dysfunction

The endothelial cell lining of the arterial vasculature is a biologically active organ. It modulates the relationship between the cellular elements of the blood and the vascular wall, mediating the normal balance between thrombosis and fibrinolysis, and plays an integral role in leukocyte/cell wall interactions. Abnormalities of endothelial function can render the arterial system susceptible to atherosclerosis and its associated adverse outcomes.

Most patients with diabetes, including those with PAD, demonstrate abnormalities of endothelial function and vascular regulation (13). The mediators of endothelial cell dysfunction in diabetes are numerous, but an important final common pathway is derangement of NO bioavailability. NO is a potent stimulus for vasodilatation and limits inflammation via its modulation of leukocyte-vascular wall interaction. Furthermore, NO inhibits vascular smooth muscle cell (VSMC) migration and proliferation and limits platelet activation. Therefore, the loss of normal NO homeostasis can result in a cascade of events in the vasculature leading to atherosclerosis and its consequent complications.

Several mechanisms contribute to the loss of NO homeostasis, including hyperglycemia, insulin resistance, and free fatty acid (FFA) production. Hyperglycemia blocks the function of endothelial eNOS and boosts the production of reactive oxygen species, which impairs the vasodilator homeostasis fostered by endothelium. This oxidative stress is amplified because, in endothelial cells, glucose transport is not downregulated by hyperglycemia.

In addition to hyperglycemia, insulin resistance plays a role in the loss of normal NO homeostasis (14). One consequence of insulin resistance is excess liberation of FFAs. FFAs may have numerous deleterious effects on normal vascular homeostasis, including activation of protein kinase C (PKC), inhibition of phosphatidylinositol (PI)-3 kinase (an eNOS agonist pathway), and production of reactive oxygen species. The sum effect of all these leads to the loss of NO homeostasis.

The effects of endothelial cell dysfunction, along with activation of the receptor for advanced glycation end products (RAGE), increase the local inflammatory state of the vascular wall, mediated in part by increased production of the transcription factors, nuclear factor-κB (NF-κB), and activator protein 1. Local increases in these proinflammatory factors, together with the loss of normal NO function is associated with increased leukocyte chemotaxis, adhesion, transmigration, and transformation into foam cells. This latter process is further augmented by increased local oxidative stress (15). Foam cell transformation is the earliest precursor of atheroma formation.

Diabetes and the VSMC

The presence of diabetes is also associated with significant abnormalities in VSMC function. Diabetes stimulates proatherogenic activity in VSMC via mechanisms similar to that in endothelial cells, including reductions in PI-3 kinase, as well as local increases in oxidative stress and upregulation of PKC, RAGE, and NF-κB. The sum total of these changes might be expected to promote the formation of atherosclerotic lesions. These effects may also increase VSMC apoptosis and tissue factor production, while reducing de novo synthesis of plaque stabilizing compounds, such as collagen. Thus, the above events accelerate atherosclerosis and are also associated with plaque destabilization and precipitation of clinical events (16).

Diabetes and the platelet

Platelets play an integral role in the connection between vascular function and thrombosis. Abnormalities in platelet biology may not only promote the progression of atherosclerosis, but also influence the consequence of plaque disruption and atherothrombosis. As in the endothelial cell, platelet uptake of glucose is unchecked in the setting of hyperglycemia and results in increased oxidative stress. Consequently, platelet aggregation is enhanced in patients with diabetes. Platelets in diabetic patients also have increased expression of glycoprotein Ib and IIb/IIIa receptors, which are important in thrombosis via their role in adhesion and aggregation.

Diabetes, coagulation, and rheology

Diabetes leads to a hypercoagulable state (17). It is associated with the increased production of tissue factor by endothelial cells and VSMCs, as well as increased plasma concentrations of factor VII. Hyperglycemia is also associated with a decreased concentration of antithrombin and protein C, impaired fibrinolytic function, and excess production of PAI-1.

Finally, abnormalities in rheology are seen in diabetic patients as an elevation in blood viscosity and fibrinogen. Elevated viscosity and fibrinogen are both correlative with abnormalities in ABI among patients with PAD, and elevated fibrinogen (or its degradation products) has been associated with the development, presence, and complications of PAD.

In summary, diabetes increases the risk for atherogenesis via deleterious effects on the vessel wall, as well as effects on blood cells and rheology. The vascular abnormalities leading to atherosclerosis in patients with diabetes may be evident before the diagnosis of diabetes, and they increase with duration of diabetes and worsening blood glucose control. Further studies of the diabetes-specific mechanisms responsible for the development of atherosclerosis, as well as the specific pathways responsible for PAD in this population, are needed.

3) HOW IS PAD IN DIABETES BEST DIAGNOSED AND EVALUATED?

Clinical evaluation: history and physical

The initial assessment of PAD in patients with diabetes should begin with a thorough medical history and physical examination to help identify those patients with PAD risk factors, symptoms of claudication, rest pain, and/or functional impairment. Alternative causes of leg pain on exercise are many, including spinal stenosis, and should be excluded. PAD patients present along a spectrum of severity ranging from no symptoms, intermittent claudication, rest pain, and finally to nonhealing wounds and gangrene.

A thorough walking history will elicit classic claudication symptoms and variations thereof. As these symptoms are of-

ten not reported, patients should be asked specifically about them. Two important components of the physical examination are visual inspection of the foot and palpation of peripheral pulses. Dependent rubor, pallor on elevation, absence of hair growth, dystrophic toenails, and cool, dry, fissured skin are signs of vascular insufficiency and should be noted. The interdigital spaces should be inspected for fissures, ulcerations, and infections (18).

Palpation of peripheral pulses should be a routine component of the physical exam and should include assessment of the femoral, popliteal, and pedal vessels. It should be noted that pulse assessment is a learned skill and has a high degree of interobserver variability, with high false-positive and false-negative rates. The dorsalis pedis pulse is reported to be absent in 8.1% of healthy individuals, and the posterior tibial pulse is absent in 2.0%. Nevertheless, the absence of both pedal pulses, when assessed by a person experienced in this technique, strongly suggests the presence of vascular disease.

Noninvasive evaluation for PAD: ABI

In contrast to the variability of pulse assessment and the often nonspecific nature of information obtained via history and other components of the physical exam, the ABI is a reproducible and reasonably accurate, noninvasive measurement for the detection of PAD and the determination of disease severity (19). The ABI is defined, as noted previously, as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure at the arm. The tools required to perform the ABI measurement include a hand-held 5–10 MHz Doppler probe and a blood pressure cuff.

The ABI is measured by placing the patient in a supine position for 5 min. Systolic blood pressure is measured in both arms, and the higher value is used as the denominator of the ABI. Systolic blood pressure is then measured in the dorsalis pedis and posterior tibial arteries by placing the cuff just above the ankle. The higher value is the numerator of the ABI in each limb.

The diagnostic criteria for PAD based on the ABI are interpreted as follows:

- Normal if 0.91–1.30
- Mild obstruction if 0.70–0.90
- Moderate obstruction if 0.40–0.69
- Severe obstruction if <0.40
- Poorly compressible if >1.30

An ABI value >1.3 suggests poorly compressible arteries at the ankle level due to the presence of medial arterial calcification. This renders the diagnosis of PAD by ABI alone less reliable.

Due to the high estimated prevalence of PAD in patients with diabetes, a screening ABI should be performed in patients >50 years of age who have diabetes. If normal, the test should be repeated every 5 years. A screening ABI should be considered in diabetic patients <50 years of age who have other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years). A diagnostic ABI should be performed in any patient with symptoms of PAD. It should be noted that in the evaluation of the individual patient there may be errors and that the reliability of any diagnostic test is dependent on the prior probability of disease (Bayes' Theorem).

Vascular lab evaluation: segmental pressures and pulse volume recordings

In the patient with a confirmed diagnosis of PAD in whom an assessment of the location and severity is desired, the next step would be a vascular laboratory evaluation for segmental pressures and pulse volume recordings (PVRs). These tests should also be considered for patients with poorly compressible vessels or those with a normal ABI where there is high suspicion of PAD. Segmental pressures and PVRs are determined at the toe, ankle, calf, low thigh, and high thigh. Segmental pressures help with lesion localization, while PVRs provide segmental waveform analysis, a qualitative assessment of blood flow.

Treadmill functional testing

For patients with atypical symptoms or a normal ABI with typical symptoms of claudication, functional testing with a graded treadmill may help with diagnosis. Patients with claudication will typically exhibit a >20-mmHg drop in ankle pressure after exercise. Treadmill testing may also be used as an evaluation of treatment efficacy and as an assessment of physical function.

Additional evaluation

In patients with possible CLI, further noninvasive studies may help with clinical decision making regarding revascularization. A toe pressure <40 mmHg or a toe waveform <4 mm may predict impaired wound healing and is often used in the evaluation of ischemic ulcers. Systolic toe pressure is also useful in the evaluation of the patient with medial arterial calcification, where the ABI is less accurate. Another method of predicting healing is the measurement of the transcutaneous partial pressure of oxygen ($TcPO_2$). A value <30 mmHg is associated with poor healing of wounds or amputations.

Anatomic studies: duplex sonography, magnetic resonance angiogram, and contrast angiography

For those patients in whom revascularization is considered and anatomical localization of stenoses or occlusions is important, an evaluation with a duplex ultrasound or a magnetic resonance angiogram (MRA) may be valuable. Duplex ultrasound can directly visualize vessels and is also useful in the surveillance of postprocedure patients for graft or stent patency. MRA is noninvasive with minimal risk of renal insult. It may give images that are comparable with conventional X-ray angiography, especially in occult pedal vessels, and may be used for anatomical diagnosis.

While MRA is a safe and promising new technology, the gold standard for vascular imaging is X-ray angiography, and it is indicated primarily for the anatomical evaluation of the patient in whom a revascularization procedure is intended. Because it is an invasive test with a small risk of contrast-induced nephrotoxicity, "exploratory" angiography should not be performed for diagnosing PAD. For patients with suspected pedal ischemia, the angiography should include an aortogram with selective unilateral runoff and a magnified lateral view of the foot. It should be noted that the decision to perform an angiogram is made on a clinical basis and the need for revascularization, sometimes independent of any prior noninvasive tests.

4) WHAT ARE THE APPROPRIATE MEDICAL TREATMENTS FOR PAD IN PEOPLE WITH DIABETES?

Treatment of systemic atherosclerosis associated with PAD

Most cardiovascular risk factors for individuals with PAD are similar to those for people with diabetes alone. Although there is little prospective data showing that treating these risk factors will improve cardiovascular outcomes in people

with both PAD and diabetes specifically, consensus strongly supports such interventions, given that both PAD and diabetes are associated with significantly increased risks of cardiovascular events.

Cigarette smoking. Cigarette smoking is the single most important modifiable risk factor for the development and exacerbation of PAD. In patients with PAD, tobacco use is associated with increased progression of atherosclerosis as well as increased risk of amputation (20). Thus, tobacco cessation counseling and avoidance of all tobacco products is absolutely essential.

Glycemic control. Hyperglycemia may be a cardiovascular risk factor in individuals with PAD; however, evidence for the benefit of tight glycemic control in ameliorating PAD is lacking. In the U.K. Prospective Diabetes Study (UKPDS), intensive glycemic control reduced diabetes-related endpoints and diabetes-related deaths (21). However, it was not associated with a significant reduction in the risk of amputation due to PAD. In fact, the major reduction in adverse end points was due to improved microvascular rather than macrovascular end points. An additional caveat is that, although it is likely that many patients with PAD were included in the UKPDS study, the prevalence of PAD was not defined, therefore conclusions from this study may not directly relate to patients with diabetes and PAD. Nevertheless, good glycemic control (A1C <7.0%) should be a goal of therapy in all patients with PAD and diabetes in order to prevent microvascular complications.

Hypertension. Hypertension is associated with the development of atherosclerosis as well as with a two- to threefold increased risk of claudication (22). In the UKPDS, diabetes endpoints and risks of strokes were significantly reduced and risk of MI was nonsignificantly reduced by tight blood pressure control (23). Risk for amputation due to PAD was not reduced. In general, the effects of treating hypertension on atherosclerotic disease or on cardiovascular events have not been directly evaluated in patients with both PAD and diabetes. Nevertheless, consensus still strongly supports aggressive blood pressure control (<130/80 mmHg) in patients with PAD and diabetes in order to reduce cardiovascular risk.

Results of the Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril, an ACE inhibitor, significantly reduced the rate of cardiovascular death, MI, and stroke in a broad range of high-risk patients without hypertension (24). Of the 9,297 patients in this study, 4,051 had PAD. Patients with PAD had a similar reduction in the cardiovascular endpoints when compared with those without PAD, thus demonstrating that ramipril was effective in lowering the risk of fatal and nonfatal ischemic events among all patients. Nonetheless, the potential benefit of ACE inhibitors has not been studied in prospective, randomized trials in patients with PAD. Such trials are needed before making definite treatment recommendations regarding the use of an ACE inhibitor as a unique pharmacologic agent in the treatment of PAD.

Dyslipidemia. Although treating dyslipidemia decreases cardiovascular morbidity and mortality in general, no studies have directly studied the treatment of lipid disorders in patients with PAD. In a meta-analysis of randomized trials in patients with PAD and dyslipidemia who were treated by a variety of therapies, Leng et al. (25) reported a nonsignificant reduction in mortality and no change in nonfatal cardiovascular events. However, the severity of claudication was reduced by lipid-lowering treatment. Similarly, in a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S), the reduction in cholesterol level by simvastatin was associated with a 38% reduction in the risk of new or worsening symptoms of intermittent claudication (26,27). In the Heart Protection Study, adults with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive simvastatin or placebo (28). A significant reduction in coronary death rate was observed in people with PAD, but the reduction was no greater than the effect of the drug on other subgroups. Thus, although there are no data showing direct benefits of treating dyslipidemia in individuals with both PAD and diabetes, dyslipidemia in diabetic patients should be treated according to published guidelines, which recommend a target LDL cholesterol level <100 mg/dl. Following this guideline, it is our belief that lipid-lowering treatment may not only decrease cardiovascular deaths, but may also slow the progression of PAD in diabetes.

Antiplatelet therapy. The Antiplatelet Trialists' Collaboration reviewed 145 randomized studies in an effort to evaluate the efficacy of prolonged treatment with antiplatelet agents (in most cases, aspirin) (29).

This meta-analysis combined data from >100,000 patients, including ~70,000 high-risk patients with evidence of cardiovascular disease. A 27% reduction in odds ratio (OR) in the composite primary endpoint (MI, stroke, and vascular death) was found for high-risk patients compared with control subjects. However, when a subset of >3,000 patients with claudication was analyzed, effects of antiplatelet therapy were not significant. Thus, the use of aspirin to prevent cardiovascular events and death in patients with PAD is considered equivocal; however, aspirin therapy for people with diabetes is recommended (30).

The Clopidogrel Versus Aspirin in Patients At Risk of Ischemic Events (CAPRIE) Study evaluated aspirin versus clopidogrel in >19,000 patients with recent stroke, MI, or stable PAD (31). The study results showed that 75 mg of clopidogrel per day was associated with a relative risk reduction of 8.7% compared with the benefits of 325 mg of aspirin per day for a composite endpoint (MI, ischemic stroke, and vascular death). More striking, in a subgroup analysis of >6,000 patients with PAD, clopidogrel was associated with a risk reduction of 24% compared with aspirin. Clopidogrel was shown to be as well tolerated as aspirin. Based on these results, clopidogrel was approved by the Food and Drug Administration (FDA) for the reduction of ischemic events in all patients with PAD. In the CAPRIE study, about one-third of the patients in the PAD group had diabetes. In those patients, clopidogrel was also superior to aspirin therapy.

In summary, patients with diabetes should be on an antiplatelet agent (e.g., aspirin or clopidogrel) according to current guidelines (30). Those with diabetes and PAD may benefit more by taking clopidogrel.

Treatment of symptomatic PAD

Medical therapy for intermittent claudication currently suggests exercise rehabilitation as the cornerstone therapy, as well as the potential use of pharmacologic agents.

Exercise rehabilitation. Since 1966, many randomized controlled trials have demonstrated the benefit of supervised exercise training in individuals with PAD

(32,33). These programs call for at least 3 months of intermittent treadmill walking three times per week. Exercise therapy has minimal associated morbidity and is likely to improve the cardiovascular risk factor profile. Of note, however, in nearly all studies, unsupervised exercise regimens have shown lack of efficacy in improving functional capacity.

Pharmacologic therapies. Pentoxifylline, a hemorheologic agent, was approved by the FDA in 1984 for treating claudication. The results of postapproval trials, however, suggest that it does not increase walking distance to a clinically meaningful extent.

Cilostazol, an oral phosphodiesterase type III inhibitor, was the second drug to gain FDA approval for treating intermittent claudication. Significant benefit has been demonstrated in increasing maximal walking time in six of eight randomized controlled trials, in addition to improving functional status and health-related quality of life (34). The use of this drug is contraindicated if any degree of heart failure is present due to concerns about arrhythmias. In a single trial, pentoxifylline was inferior when compared with treatment with cilostazol (35). Based on the above, cilostazol is the drug of choice if pharmacologic therapy is necessary for the management of PAD in patients with diabetes.

Preventative foot care. All patients with diabetes and PAD should receive preventive foot care with regular supervision to minimize the risks of developing foot complications and limb loss (18).

Treatment of the ischemic foot

CLI manifested by rest pain, ulceration, or gangrene in the foot of a person with diabetes portends limb loss and requires urgent treatment. The frequent presence of neuropathy strongly influences the clinical presentation. The presence of neuropathy blunts pain perception, allowing a later presentation with more severe lesions than in the nondiabetic patient. In a vicious cycle, the presence of PAD increases nerve ischemia, resulting in worsened neuropathy. In addition, such arterial lesions may progress undetected for long intervals due to the distal distribution, making the severity of the underlying PAD often underestimated. Accordingly, diabetic patients with PAD are more likely to present with advanced disease compared with nondiabetic patients (36).

The "neuroischemic" foot—with PAD and neuropathy—is more prone to traumatic ulceration, infection, and gangrene. Each complication requires specific management as well as treatment of the underlying ischemia.

In contrast to the plantar location of neuropathic ulcers, ischemic ulcers are commonly seen around the edges of the foot, including the apices of the toes and the back of the heel. They are generally associated with a pivotal event: trauma or wearing unsuitable shoes. Important aspects of conservative management include debridement, offloading the ulcer, appropriate dressings, and adjunctive wound healing techniques (37).

Prompt and timely referral of the patient to appropriate foot care and vascular specialists is critical.

Debridement. Debridement should remove all debris and necrotic material to render infection less likely. The preferred method is frequent sharp debridement with a scalpel, normally undertaken at the hospital bedside or in the outpatient setting. Indications for surgical debridement include the presence of necrotic tissue, localized fluctuance, and drainage of pus or crepitus with gas in the soft tissues on X-ray.

Footwear. With the neuroischemic foot, the chief aim is to protect the foot from pressure and shear. Ulcers may be prevented from healing if the patient wears tight shoes or slip-on styles. It is most important that the shoe does no harm. A shoe that is sufficiently long, broad and deep, and fastens with a lace or strap high on the foot may be all that is needed to protect the margins of the foot and allow healing of the ulcers. It may be necessary, however, to provide special footwear, such as sandals or braces.

Dressings. Nonadherent dressings should cover diabetic foot ulcers at all times. No single ideal dressing exists, and there is no evidence that any one dressing is better for the diabetic foot than any other. However, the following properties are desirable: ease of removal from the foot and ability to accommodate pressures of walking without disintegrating. Occlusive dressings may lower the risk of infection.

Treatment of infection

Although ulcers often become infected, the signs and symptoms of foot infection are diminished in diabetic patients. The early warning signs of infection may be subtle because of an impaired neuroinflammatory response. Furthermore, it may be difficult to differentiate between the erythema of cellulitis and the rubor of ischemia. The redness of ischemia, which is most marked on dependency, will disappear upon elevation of the limb, whereas that of cellulitis will remain irrespective of foot position. Infections in the diabetic foot are often polymicrobial; broad spectrum antibiotics are initially indicated. Severe infections require intravenous antibiotic therapy and urgent assessment of the need for surgical drainage and debridement.

Both wet and dry gangrene can occur in the neuroischemic foot. Wet gangrene is caused by a septic arteritis, secondary to soft-tissue infection or ulceration. Gas in the soft tissues is a serious finding requiring an immediate trip to the operating room for open drainage of all infected spaces and intravenous broad-spectrum antibiotics. It is important to emphasize that medical treatment of infection with antibiotics alone is insufficient to resolve the majority of diabetic foot infections.

Incision and drainage is the basic tenet of treatment for nearly all infections of the diabetic foot. Sometimes amputation of a toe, toes, or ray(s) may be necessary to establish drainage. Salvage of the diabetic foot is usually possible but may require aggressive debridement and revascularization. Postoperatively there may be considerable tissue deficit or exposure of bone or tendon. In such circumstances the foot should be revascularized as indicated and soft tissue deficits may be repaired by reconstructive surgery at a latter stage. A vacuum-assisted wound closure device provides topical subatmospheric pressure that is most helpful in staged procedures.

Dry gangrene is secondary to a severe reduction in arterial perfusion and occurs in chronic critical ischemia. Revascularization should be initially carried out followed by surgical debridement. If revascularization is not possible, surgical debridement or amputation should be considered if the necrotic toe or any other area of necrosis is painful or if the circulation is not severely impaired. Otherwise the necrosis should be allowed to autoam-

putate as a surgical procedure may result in further necrosis and a higher level of amputation.

Indications for revascularization

The indications for limb revascularization are disabling claudication or CLI (rest pain or tissue loss) refractive to conservative therapy. Disabling claudication is a relative, not absolute indication, and requires significant patient consultation. One must weigh existing symptoms against the risk of the procedure and its expected effect and durability. Although most ischemic limbs can be revascularized, some cannot. Lack of a target vessel, unavailability of autogenous vein, or irreversible gangrene beyond the midfoot may preclude revascularization. In such patients a choice must be made between prolonged medical therapy and primary amputation.

Two general techniques of revascularization exist: open surgical procedures and endovascular interventions. The two approaches are not mutually exclusive and may be combined, such as iliac angioplasty combined with infrainguinal saphenous vein bypass. The risks, expected benefit, and durability of each must be considered. In either approach, meticulous technique, flexibility and resourcefulness of judgement, and contingency plans are important. Appropriate patient preparation, intra-procedure monitoring, and postprocedure care will minimize complications.

Endovascular intervention is more appropriate in patients with focal disease, especially stenosis of larger more proximal vessels, and when the procedure is performed for claudication. Open procedures have been successfully carried out for all lesions and tend to have greater durability. However, open procedures are associated with a small but consistent morbidity and mortality. The choice between the two modalities in an individual patient is a complex decision and requires team consultation.

Aortoiliac disease is traditionally and effectively treated with prosthetic aortofemoral bypass but is increasingly amenable to endovascular angioplasty and stenting. Although percutaneous angioplasty and stenting have achieved their best results in the aortoiliac vessels, open revascularization probably offers results that are more durable when diffuse aortoiliac disease or occlusion is present.

Stenoses of the superficial femoral artery may be treated with an endovascular approach, but restenosis is common. More durable results appear obtainable with open bypass to the popliteal artery, particularly using saphenous vein. Whether newer endovascular techniques, such as stents to prevent restenosis, will affect the longer-term outcome of endovascular management of superficial femoral artery occlusions remains speculative.

Bypass to the tibial or pedal vessels with autogenous vein has a long track record in limb salvage and remains the most predictable method of improving blood flow to the threatened limb. The procedure is safe, durable, and effective. Below the knee bypass accounts for 75% of infrainguinal procedures in patients with diabetes, with the anterior tibial/dorsalis pedis artery the most common target vessel. Indeed, surgical bypass with greater saphenous vein has become the procedure of choice for patients with diabetes and tibial disease.

Advances in endovascular therapy, particularly smaller instrumentation and standardization of thrombolytic therapy for periprocedural thromboses, have allowed more aggressive use of tibial angioplasty. Despite this increased use, however, the efficacy of tibial angioplasty remains uncertain. Nonetheless, it may provide a means to "buy time" to allow a patient to heal and recover from a limb-threatening situation.

The morbidity and mortality of vascular surgical procedures in patients with diabetes has improved significantly with a protocol of preoperative risk assessment and perioperative risk management, especially with the use of β-blockers. The outcomes are now comparable with those of nondiabetic vascular patients. The choice of preoperative coronary artery bypass grafts (CABGs) is not encouraged, as the risk of two procedures (CABG and leg bypass) exceeds the risk of leg bypass alone. The decision for CABG should be based on the same indications as for the nonoperative patient.

Regular postoperative follow-up is mandatory because most late revascularization failures involve progression of intimal hyperplasia at areas of anastomosis, vein injury, valve sites, or angioplasty. History, clinical exam, and the ABI are simple and effective methods of detecting major restenosis but may miss silent lesions that may progress to sudden thromboses if uncorrected. These lesions are best detected by duplex ultrasonography. In addition, ~50% of patients with CLI in one limb will develop threatened limb loss in the contralateral limb, underscoring the need for ongoing risk factor reduction and close monitoring of lower-limb circulation.

Major amputation in the neuroischemic foot is necessary and indicated only when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis secondary to a major arterial occlusion has destroyed the foot. Using these criteria, the number of major limb amputations should be limited.

Most amputations can be prevented and limbs salvaged through a multiarmed treatment of antibiotics, debridement, revascularization, and staged wound closure. On the other hand, amputation may offer an expedient return to a useful quality of life, especially if a prolonged course of treatment is anticipated with little likelihood of healing. Diabetic patients should have full and active rehabilitation following amputation. Decisions should be made on an individual basis with rehabilitative and quality-of-life issues considered highly.

CONCLUSIONS — In summary, PAD is a common cardiovascular complication in patients with diabetes. In contrast to PAD in nondiabetic individuals, it is more prevalent and, because of the distal territory of vessel involvement and its association with peripheral neuropathy, it is more commonly asymptomatic.

Patients with PAD and diabetes thus may present later with more severe disease and have a greater risk of amputation. Moreover, the presence of PAD is a marker of excess cardiovascular risk.

It is important to diagnose PAD in patients with diabetes to elicit symptoms, prevent disability and limb loss, and identify a patient at high risk of MI, stroke, and death. The diagnosis is made with a determination of the ABI. It is recommended that patients with diabetes who are >50 years of age have an ABI performed. An ABI is also useful in patients with other PAD risk factors and in those with symptoms.

Treatment of the patient with diabetes and PAD should be twofold: *1*) primary and secondary CVD risk factor

modification and 2) treatment of PAD symptoms (claudication and critical limb ischemia) and limiting progression of disease.

It is the hope of this panel that by arriving at a consensus of the fundamentals of assessment and management of this devastating complication of diabetes, we may effect more uniformity of care and achieve better outcomes for our patients with diabetes. We also strongly encourage clinicians to function cooperatively and effectively as teams of specialists in the management of this complex patient population, with the common goal of reducing vascular events—MI, stroke, and amputation—that too often result in disability, social decline, and death.

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APPENDIX

Consensus panel

Peter Sheehan, MD, Chair; Michael Edmonds, MD; James L. Januzzi, Jr., MD, FACC (American College of Cardiology); Judith Regensteiner, PhD; Lee Sanders, DPM; and Mellick Sykes, MD.

Presenters at the conference

Christopher E. Attinger, MD; Joshua Beckman, MD, FACC; Michael Criqui, MD, MPH; James B. Froelich, MD, MPH; John M. Giurini, DPM; Linda Haas, PhC, RN, CDE; Allen Hamdan, MD; Larry Harkless, DPM; Michael R. Jaff, DO; Ishwarlal Jialal, MD, PhD; Frank LoGerfo, MD; Emile R. Mohler, MD; Jeffrey Olin, DO, FACP, FACC; Michael Pinzur, MD; Gayle E. Reiber, MPH, PhD; Kenneth Rosenfield, MD; Solomon Tesfaye, MD, FRCP; Aristidis Veves, MD; and E. Kent Yucel, MD.

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