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STATE-OF-THE-ART PAPER

Peripheral Arterial Disease in Patients With Diabetes

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Peripheral arterial disease (PAD) is a chronic, lifestyle-limiting disease and is an independent predictor of cardiovascular and cerebrovascular ischemic events. Despite the recognition that PAD is associated with a marked increase in the risk of ischemic events, this particular manifestation of systemic atherosclerosis is largely underdiagnosed and undertreated. The risk of PAD is markedly increased among individuals with diabetes, and ischemic event rates are higher in diabetic individuals with PAD than in comparable non-diabetic populations. Consequently, early diagnosis and treatment of PAD in patients with diabetes is critically important in order to reduce the risk of cardiovascular events, minimize the risk of long-term disability, and improve quality of life. A diagnosis of PAD in patients with diabetes mandates a multi-faceted treatment approach, involving aggressive risk-factor modification, antiplatelet therapy, and revascularization procedures. The American Diabetes Association recently issued a consensus statement on the epidemiology, pathophysiology, diagnosis, and management of PAD in patients with diabetes. This article will review the clinical implications of the consensus statement and highlight the treatment options available in order to help prevent future ischemic events in diabetic individuals with PAD. (J Am Coll Cardiol 2006;47: 921–9) © 2006 by the American College of Cardiology Foundation

Atherosclerosis is a progressive process affecting multiple vascular beds; its clinical consequences, which include coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD), are potentially life-threatening (1). Atherosclerotic disease in one vascular bed indicates possible disease in others (2).

The risk of atherosclerotic disease is markedly increased among individuals with diabetes. The increased risk is independent of, and additive to, other cardiovascular risk factors. Atherosclerosis causes most of the death and disability in patients with diabetes, particularly in the type 2 diabetic patient population (3). The Verona Diabetes Study showed that cardiovascular disease is responsible for 44% of all-cause fatalities in the diabetic patient population (4). The duration of diabetes increases the risk of death from cardiovascular disease, independent of co-existing risk factors (5). Insulin resistance is a key factor in the pathogenesis of diabetes. Insulin resistance and its attendant metabolic abnormalities may cause much of the increased cardiovascular risk of diabetes (6).

Epidemiological studies have confirmed an association between diabetes and an increased prevalence of PAD (7,8). Peripheral arterial disease is usually characterized by occlusive arterial disease of the lower extremities. Although many patients are asymptomatic, or have atypical exertional symptoms, approximately one-third experience intermittent claudication, described as aching, cramping, or numbness in the affected limb, occurring with exercise and relieved at rest (9). Peripheral arterial disease in patients with diabetes adversely affects quality of life (10) and is associated with substantial functional impairment (11). The reduced walking speed and distance associated with intermittent claudication may result in progressive loss of function and long-term disability (12,13). With more severe disease, critical limb ischemia (CLI) may develop, resulting in ischemic ulceration of the foot and risk of limb loss (14,15). Importantly, PAD is associated with a substantial increase in the risk of fatal and non-fatal cardiovascular and cerebrovascular events, including myocardial infarction (MI) and stroke (16,17). Patients with diabetes and PAD are at higher risk of lower extremity amputation than those without diabetes (18). Furthermore, cardiovascular and cerebrovascular event rates are higher in diabetic individuals with PAD than in comparable non-diabetic populations (12).

Although much is known about PAD in the general population, the management of PAD in those with diabetes is less clear. Recently, the American Diabetes Association (ADA) issued a consensus statement that provides guidelines for the diagnosis and management of PAD in patients with diabetes (12). The purpose of this article is to review the consensus statement and to discuss the treatment options available to help prevent future ischemic events in diabetic individuals with PAD. Patients with diabetes are clearly a high-risk group of individuals who are at risk of developing extensive vascular disease requiring a multi-discipline approach. Cardiovascular healthcare providers have a unique opportunity to reduce the disease burden in this population.

EPIDEMIOLOGY

Peripheral arterial disease affects approximately 12 million people in the U.S.; approximately 20% to 30% of these patients have diabetes. However, accurate assessment of the preva-

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Abbreviations and Acronyms

ABCD = Appropriate Blood Pressure Control in Diabetes trial
ABI = ankle-brachial index
ADA = American Diabetes Association
CAD = coronary artery disease
CARDS = Collaborative AtoRvastatin Diabetes Study
CLI = critical limb ischemia
CRP = C-reactive protein
CTA = computed tomographic angiography
FDA = Food and Drug Administration
LDL = low-density lipoprotein
MI = myocardial infarction
MRA = magnetic resonance angiography
NO = nitric oxide
PAD = peripheral arterial disease
UKPDS = United Kingdom Prospective Diabetes Study

lence of PAD in the diabetic population is confounded by various factors: the condition is often asymptomatic; peripheral neuropathy may alter pain perception; and two of the common clinical findings, the absence of peripheral pulses and the presence of claudication, are inadequate diagnostic indicators (12). In studies using the ankle-brachial index (ABI), which is the preferred screening technique, the prevalence of PAD (defined as an ABI <0.90) in diabetic individuals ranges from 20% to 30% (19–21).

The duration and severity of diabetes correlates with the incidence and extent of PAD (18). In a prospective cohort study, Al-Delaimy et al. (22) found a strong positive association between the duration of diabetes and the risk of developing PAD. The association was particularly strong among men with hypertension or who were current smokers. Adler et al. (23) estimated the prevalence of PAD up to 18 years after the diagnosis of diabetes in 4,987 subjects (United Kingdom Prospective Diabetes Study [UKPDS]). The data showed a higher prevalence of PAD in those with longer duration of diabetes. The degree of diabetic control is an independent risk factor for PAD; with every 1% increase in glycosylated hemoglobin, the risk of PAD has been shown to increase by 28% (24). The risk of PAD is associated with advancing age and the presence of peripheral neuropathy (12). In addition, the risk is higher in those of African-American or Hispanic descent compared with non-Hispanic white individuals, even after adjustment for other known risk factors and the increased prevalence of diabetes in these populations. In a community-based study, African-American subjects had a lower mean ABI and a greater prevalence of PAD than their non-Hispanic white counterparts (25).

Patients with diabetes more commonly develop symptomatic PAD. In the Framingham study, the presence of diabetes increased the risk of intermittent claudication by 3.5-fold in men and 8.6-fold in women (26). Furthermore, patients with diabetes and PAD are more likely to present with an ischemic ulcer or gangrene than patients without diabetes, increasing the risk of lower-extremity amputation (18). Faglia et al. (27) observed a positive trend between PAD severity and amputation rate in patients with diabetes. People with diabetes are 15 times more likely to have an amputation than those without (28), and an annual amputation incidence rate of 0.6% has been reported in these patients (29,30).

PATHOPHYSIOLOGY

The pathophysiology of PAD in the diabetic population is similar to that in the non-diabetic population. However, the distribution of peripheral atherosclerosis in patients with PAD and diabetes is often more distal than in patients without diabetes, and commonly involves the tibial vessels (31).

The abnormal metabolic state that accompanies diabetes directly contributes to the development of atherosclerosis; proatherogenic changes include increases in vascular inflammation and alterations in multiple cell types (3).

Inflammation is an established risk factor for the development of atherosclerosis. Elevated levels of C-reactive protein (CRP) are strongly associated with the development of PAD. Furthermore, CRP levels are abnormally elevated in patients with impaired glucose tolerance (32). In addition to being a marker of atherosclerosis, elevated levels of CRP may also be a risk factor for PAD. C-reactive protein has procoagulant effects related to its ability to enhance expression of tissue factor (33). C-reactive protein also inhibits endothelial cell nitric oxide (NO) synthase, resulting in abnormal regulation of vascular tone, and increases production of plasminogen activator inhibitor-1, which inhibits the formation of fibrinolytic plasmin from plasminogen (12,34).

Most patients with diabetes and PAD demonstrate generalized endothelial cell dysfunction. In healthy vessels, endothelial cells synthesize NO, a potent vasodilator that inhibits platelet activation and vascular smooth muscle cell migration. Diabetes impairs NO-mediated vasodilatation (35). A number of mechanisms contribute to the decreased bioavailability of endothelium-derived NO in diabetes, including hyperglycemia, excess free fatty acids, and insulin resistance (36,37). The effects of endothelial cell dysfunction increase arterial susceptibility to atherosclerosis.

In addition to reducing NO concentrations, diabetes increases the production of vasoconstrictors, such as endothelin-1, which increase vascular tone and vascular smooth muscle cell growth and migration. Diabetes also stimulates other atherogenic pathways in vascular smooth muscle cells. For example, hyperglycemia activates protein kinase C and nuclear factor kappa-B, increasing the production of reactive oxygen species that promote the formation of atherosclerotic lesions (38). Vascular smooth muscle cells cultured from patients with diabetes demonstrate enhanced migration, an important step in the progression to advanced plaque formation (39). These cells strengthen the atheroma, making it less likely to rupture and cause thrombosis. However, Fukumoto et al. (40) demonstrated that

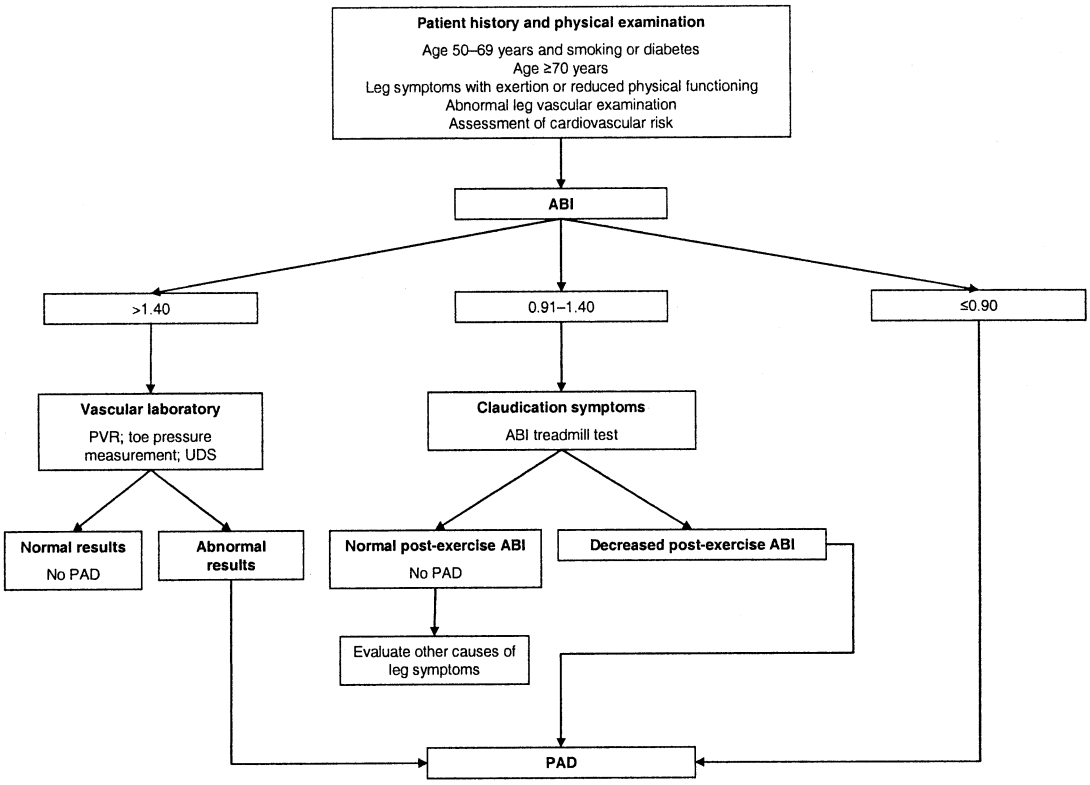

Figure 1. Typical protocol for the diagnosis of peripheral arterial disease in patients with diabetes. Reprinted with permission from N Engl J Med 2001;344:1608–21. Copyright © 2001 Massachusetts Medical Society. All rights reserved. ABI = ankle-brachial index; PAD = peripheral arterial disease; PVR = pulse-volume recording; UDS = ultrasonic duplex scanning.

advanced plaques in diabetic individuals have fewer smooth muscle cells than healthy controls; it is believed that hyperglycemia-induced lipid modifications regulate the apoptosis of vascular smooth muscle cells in advanced atherosclerotic lesions, promoting plaque instability and precipitation of clinical events (41).

Platelet aggregation is enhanced in diabetes. Elevated glucose levels activate protein kinase C, decrease production of platelet-derived NO, and increase oxidative stress. In diabetes, platelets also have increased expression of glycoprotein Ib and IIb/IIIa receptors, enhancing their thrombotic potential (34). In addition to potentiating platelet aggregation, diabetes augments blood coagulability by increasing the expression of tissue factor and decreasing levels of anticoagulants, such as antithrombin III. Consequently, it is more likely that atherosclerotic plaque rupture will result in thrombus formation (42).

Thus, alterations in metabolism in diabetes adversely affect multiple cell types within the vascular wall. The increased tendency towards coagulation, coupled with impaired fibrinolysis, contributes to the enhanced thrombotic potential characteristic of diabetes.

DIAGNOSIS

The main reasons to diagnose PAD in diabetic individuals are to initiate therapies that decrease the risk of atherothrombotic events, improve quality of life, and decrease disability. A diagnosis of PAD indicates the presence of systemic atherosclerosis that confers additional cardiovascular risk to the patient with diabetes, and gives further impetus to aggressively manage vascular risk factors in this high-risk group. A typical protocol for the diagnosis of PAD is shown in Figure 1.

A thorough medical history and physical examination are of primary importance 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. The clinical stage of symptomatic PAD can be classified using the Fontaine staging system (17). Fontaine stage I represents those who have PAD but are asymptomatic; stages IIa and IIb include patients with mild and moderate-to-severe intermittent claudication, respectively; those with ischemic rest pain are classified in Fontaine stage III; and patients with distal ulceration and gangrene represent Fontaine stage IV. A typical history of claudication has a low sensitivity, but a high specificity for PAD (43). 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 (12); pulses should be 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

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dorsalis pedis artery (44). The absence of both the dorsalis pedis pulse and the posterior tibial pulse strongly suggests the presence of PAD, but further diagnostic testing is required to confirm the diagnosis.

ABI screening. Although physical examination provides important information, additional non-invasive testing is necessary to ensure the diagnosis. The ABI is a reproducible and reasonably accurate measurement for the detection of PAD. The ABI is defined as the ratio of the ankle systolic blood pressure divided by the brachial systolic blood pressure, and is normally between 1.00 and 1.40 (45). In PAD, the ankle systolic blood pressure is less than the brachial systolic blood pressure, and the ABI is reduced to <1.00; PAD is defined as an ABI <0.90. Lower ABI values indicate more severe PAD and a higher risk of cardiovascular events. In the primary care setting, Mohler et al. (46) assessed perceptions of the ABI among 886 clinicians; most believed the ABI was useful in the diagnosis of both symptomatic (96%) and asymptomatic (89%) PAD (46).

The ADA consensus statement recommends that a screening ABI be performed in all diabetic individuals >50 years of age. If normal (0.91 to 1.40), the test should be repeated every five years. A screening ABI should be performed in any patient with symptoms of PAD (12). Ankle-brachial index determinations may be of limited value in some patients with diabetes, because calcification of the tibial arteries may render them non-compressible, resulting in unusually high ABI values (>1.40) (47). Under these conditions, the ABI cannot distinguish patients who have arterial occlusion from those who do not, making the ABI unreliable (16,44). However, an elevated ABI is still predictive of an increased risk of cardiovascular events, and other non-invasive vascular tests should be considered to make the diagnosis of PAD (48).

The ABI screening recommendations from the ADA consensus statement should be incorporated into clinical practice for the following reasons. First, an abnormal ABI is strongly associated with heightened risk for coronary heart disease mortality and morbidity. If not performed previously, screening for concomitant CAD should be considered on the basis of other clinical indicators of cardiac ischemia (e.g., angina). Second, if PAD is confirmed, an aggressive secondary prevention medical strategy is warranted. The National Cholesterol Education Program/Adult Treatment Panel III guidelines classify diabetes as a coronary heart disease equivalent and recommend a targeted low-density lipoprotein (LDL) cholesterol level of ≤100 mg/dl (49). A recent update to these guidelines suggests a target LDL level of ≤70 mg/dl for very high-risk patients (50). This recommendation was based on emerging data from the Heart Protection Study (51) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (52) which suggest a lower LDL target in patients with established coronary vascular disease and a major additional risk factor, such as diabetes. On the basis of this recommendation, it is reasonable to suggest that diabetic individuals with documented PAD, independent of symptoms, be treated to an LDL target of 70 mg/dl, but specific clinical trials would need to be performed to fully substantiate this recommendation. Third, PAD is underdiagnosed in the primary care setting, and this is an important barrier for the optimal secondary prevention of ischemic cardiovascular disease (20). Lastly, many individuals have rather atypical claudication symptoms. A large-scale PAD screening study demonstrated that only one-third of patients with documented PAD had classical claudication symptoms (43). The remaining patients either had atypical symptoms or were asymptomatic. These data suggest that classical claudication symptoms are not a reliable indicator for PAD and are inadequate in determining a person's health status due to PAD.

In the patient with a confirmed PAD diagnosis in whom further investigation is required (usually in the context of planning a revascularization procedure), the next step would be a vascular laboratory evaluation for segmental pressure and pulse volume recordings. Both hemodynamic tests aid in the localization of arterial occlusive lesions (12,44). Other non-invasive 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 (i.e., when considering various revascularization options). Ultrasonic duplex scanning can directly visualize vessels, providing information on artery wall thickness, degree of flow turbulence, and changes in blood flow velocity (53). Comprehensive imaging of the peripheral vasculature has traditionally been possible only with invasive conventional angiography. However, with the introduction of MRA and computed tomographic angiography (CTA), non-invasive imaging is now a reality (54). Contrast-enhanced MRA produces images that are comparable with conventional angiography (55). Recently, the development of CTA has dramatically improved image quality and expanded the applications for non-invasive angiography; consequently, The CTA is replacing conventional angiography in many PAD imaging studies (56).

MANAGEMENT

Once diabetic individuals with PAD have been identified, the aim of medical management is to aggressively modify cardiovascular risk factors and to prescribe antiplatelet therapy. It is also important to relieve the symptoms of intermittent claudication in order to improve functional status and quality of life.

Risk factor modification. Atherosclerotic risk factors for PAD include cigarette smoking, diabetes, dyslipidemia, and hypertension. Treatment goals are summarized in Table 1.

CIGARETTE SMOKING. Cigarette smoking is the most important risk factor for the development and progression of PAD. The amount and duration of tobacco use correlate directly with the development and progression of PAD (57). Smoking cessation increases long-term survival in patients

Table 1. Risk Factors and Treatment Goals for Patients With Diabetes and PAD

Risk Factor	Relative Risk Increase for PAD	Treatment Goal
Smoking	2.5	Cessation
Diabetes	4.0	Glycosylated hemoglobin <7%
Dyslipidemia	1.1 (per 10 mg/dl increase)	Low-density lipoprotein <100 mg/dl*
Hypertension	1.5	Blood pressure <130/80 mmHg

*Consider <70 mg/dl.
PAD = peripheral arterial disease.

with PAD. In one study, the 10-year survival rate was 82% in former smokers compared with 46% in continuing smokers (58).

An effective method of smoking cessation is nicotine replacement therapy in combination with the oral antidepressant bupropion (59). Jorenby et al. (60) conducted a double-blind, placebo-controlled comparison of sustained-release bupropion (244 subjects), a nicotine patch (244 subjects), bupropion and a nicotine patch (245 subjects), and placebo (160 subjects) for smoking cessation. The abstinence rates at 12 months were 15.6% in the placebo group, compared with 16.4% in the nicotine-patch group, 30.3% in the bupropion group ($p < 0.001$), and 35.5% in the group given bupropion and the nicotine patch ($p < 0.001$). Although abstinence rates were higher with combination therapy than with bupropion alone, the difference was not statistically significant. In a recent trial, a combination of physician advice, nicotine replacement therapy, and counseling has been shown to improve long-term mortality (61).

DIABETES. Data to support aggressive glycemic control to reduce the cardiovascular risk associated with PAD are lacking. In the UKPDS, there was evidence that intensive glycemic control with a sulphonylurea or insulin produced a non-significant 16% risk reduction for MI and sudden death compared with conventional diabetic control with diet (62). However, there were no significant differences in diabetes-related mortality or all-cause mortality between the intensive and conventional groups. Most of the risk reduction in the "any diabetes-related" aggregate end point was due to a 25% reduction in microvascular end points (retinopathy, vitreous hemorrhage, or renal failure) rather than macrovascular end points (MI, sudden death, stroke, amputation, or death due to PAD). Current guidelines from the ADA recommend a target glycosylated hemoglobin level of <7.0% in diabetic individuals in order to prevent microvascular complications (63). It should be noted that the current recommendations for glucose control from the ADA consensus statement are not based on clinical trial evidence in patients with diabetes and PAD. Further study is warranted in this population, in particular with agents that improve insulin sensitivity.

DYSLIPIDEMIA. Several large trials with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors have demonstrated significant reductions in cardiovascular event rates in patients with PAD and co-existing CAD (52,64). Lipid-lowering therapy also decreases cardiovascular events in diabetes. Indeed, patients with diabetes may experience greater risk reduction by lipid lowering than non-diabetic individuals. In the Scandinavian Simvastatin Survival Study, simvastatin reduced the risk of total mortality by 43% in patients with diabetes compared with 29% in those without the disease (65). Although there are no direct data on treating dyslipidemia in patients with both diabetes and PAD, published guidelines recommend a target LDL cholesterol level of <70 mg/dl in this very high-risk group (50). The ADA consensus statement recommends a target LDL cholesterol level of <100 mg/dl (12). As previously stated, we acknowledge the discrepancy between the published guidelines and the ADA consensus statement, but in the absence of clinical trial data, we would recommend an LDL cholesterol target of 70 mg/dl in patients with diabetes and PAD.

Recently, the Collaborative AtoRvastatin Diabetes Study (CARDS) (66) evaluated the efficacy of atorvastatin for the primary prevention of cardiovascular events in 2,838 patients with diabetes and at least one other risk factor for CAD, but without elevated LDL cholesterol levels. The risk of reaching the primary end point of a first acute major cardiovascular event was reduced by 37% with atorvastatin relative to placebo. The CARDS study validated an aggressive approach to lipid management for the primary prevention of cardiovascular events in patients with diabetes at risk for CAD, irrespective of pre-treatment LDL cholesterol levels.

HYPERTENSION. Hypertension increases the high risk of cardiovascular disease associated with diabetes. However, the role of intensive blood pressure control in patients with diabetes and PAD has not been established. In a recent study, blood-pressure lowering in normotensive patients with diabetes and PAD was particularly effective in preventing cardiovascular events (67). The UKPDS showed that although diabetes end points were significantly reduced by tight blood-pressure control, there was no effect on the risk of amputation due to PAD (68). Nevertheless, a marked reduction in vascular events with aggressive hypertension management has been demonstrated in diabetic individuals (69). The ADA consensus supports aggressive blood-pressure control (<130/80 mm Hg) in patients with diabetes and PAD to reduce cardiovascular risk (12). Studies, such as the Hypertension Optimal Treatment trial and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, have suggested that a lower target blood pressure may be beneficial (69,70). The ABCD trial demonstrated improved outcomes (particularly non-fatal MI) for patients with PAD and diabetes who achieved a blood pressure of <125/75 mm Hg compared with 135/85 mm Hg (70).

Antiplatelet therapy. In addition to the established risk factors, the risk of cardiovascular morbidity and mortality in

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PAD patients with diabetes also relates to platelet activity and inflammation. Platelet activity can be modified by the use of antiplatelet agents. The treatment goal is to prevent thrombus formation and the resultant vascular events.

A meta-analysis of 145 prospective controlled trials of antiplatelet therapy (mainly aspirin) has been reported by the Antiplatelet Trialists' Collaboration (71). This analysis combined data from >100,000 patients, including approximately 70,000 high-risk patients with evidence of cardiovascular disease, including PAD. There was a 27% reduction in the odds ratio in the composite primary endpoint of MI, stroke, and vascular death in patients taking antiplatelet therapy compared with control subjects. However, when a subset of >3,000 patients with claudication was analyzed, treatment was beneficial for the reduction of cardiovascular events, but not statistically significant. The equivocal nature of these results led the Food and Drug Administration (FDA) to conclude there was insufficient evidence to approve the use of aspirin for the secondary prevention of atherosclerotic events in patients with PAD (72); nonetheless, its use in these patients has received a guideline recommendation (73). Furthermore, aspirin has been shown to significantly improve vascular graft patency in >3,000 patients with PAD treated with bypass surgery or peripheral angioplasty (74). Aspirin at dosages of 80 to 325 mg/day is recommended for all diabetic individuals >21 years of age (75), but this recommendation is also not fully supported by clinical trial evidence. Thus, aspirin has an established role in secondary prevention in patients at high risk, with clinical evidence of either CAD or stroke. However, the role of aspirin in other populations, such as in patients with either PAD or diabetes, without clinical evidence of CAD or stroke, has not been established.

Clopidogrel, an adenosine diphosphate receptor antagonist, has potent antiplatelet activity. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study (76) was the first to evaluate aspirin versus clopidogrel in patients with recent stroke, recent MI, or established PAD. The study compared clopidogrel at 75 mg/day with aspirin at 325 mg/day in >19,000 patients (approximately 20% with diabetes). Patients treated with clopidogrel had an annual 5.32% risk of stroke, MI, or vascular death compared with a 5.83% risk in those treated with aspirin. This represented a significant 8.7% relative-risk reduction in favor of clopidogrel ($p = 0.043$). In a subset analysis of 6,452 patients with PAD, clopidogrel recipients had a 23.8% relative-risk reduction compared with aspirin recipients ($p = 0.0028$) (Fig. 2), with an annual event rate of 3.71% compared with 4.86%. Furthermore, in the PAD subgroup, approximately one-third of the patients had diabetes; in these patients, clopidogrel was also superior to aspirin (77). On the basis of these results, clopidogrel was approved by the FDA for the reduction of ischemic events in patients with PAD. The ADA consensus recommends that patients with diabetes should be on an antiplatelet agent, and that those with PAD may benefit more by taking clopidogrel than aspirin (12).

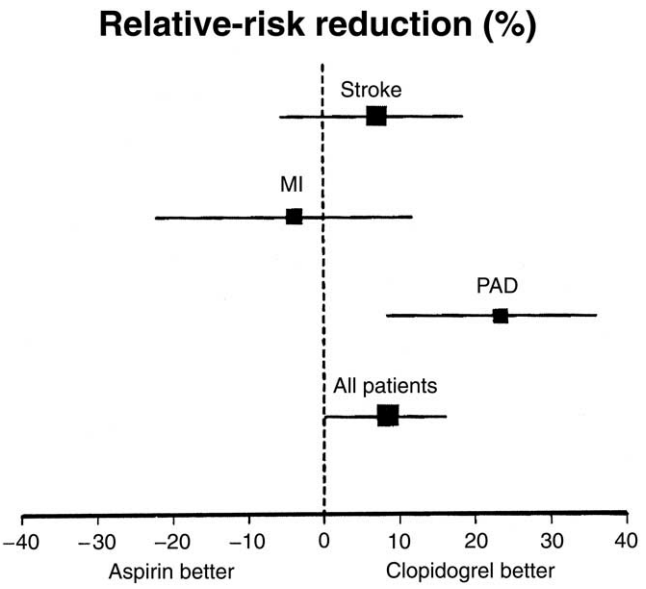

Figure 2. Relative-risk reduction and 95% confidence interval by disease subgroup in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. MI = myocardial infarction; PAD = peripheral arterial disease. Reprinted with permission from Elsevier (Lancet 1996; 348:1329–39).

Symptomatic PAD. To relieve the symptoms of intermittent claudication, patients should exercise regularly. The best results with exercise therapy are achieved under supervision, and should consist of repetitive daily walks with intermittent periods of rest and weekly increases in walking time and distance (14,78). Drug therapy can be added as adjunctive treatment to an exercise program, although this combination has not been well studied (55).

Currently, two medications are approved in the U.S. for the symptomatic treatment of intermittent claudication: pentoxifylline and cilostazol. Pentoxifylline, a hemorrheological agent, decreases blood viscosity and improves erythrocyte flexibility (79). 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 (80). Cilostazol, a phosphodiesterase inhibitor, is probably the most effective agent available in the U.S. Cilostazol (100 mg twice daily) has been shown to improve maximal walking distance by 40% to 50% compared with placebo (81,82). 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 (107, 64, and 65 m, respectively) (Fig. 3) (83). Because of concerns about the potential risk of mortality, cilostazol is contraindicated if any degree of systolic or diastolic heart failure is present (12).

Various studies have evaluated prostacyclin, prostacyclin analogues (iloprost and beraprost), and intravenous infusion of prostaglandin E_1 for the treatment of intermittent clau-

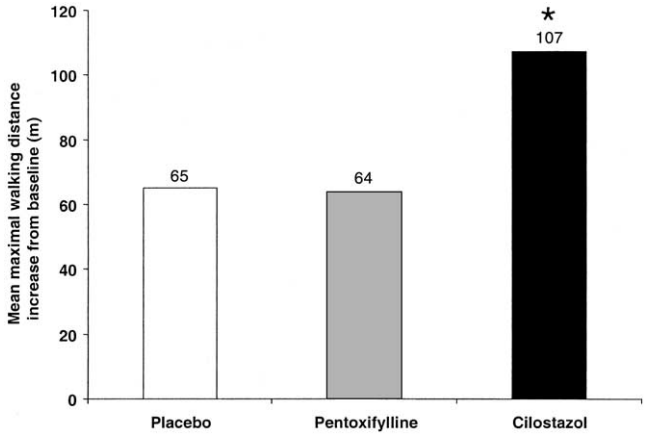

Figure 3. The mean maximal walking distance increase from baseline in patients with peripheral arterial disease after 24 weeks of treatment with placebo (n = 239), pentoxifylline 400 mg three times daily (n = 232), or cilostazol 100 mg twice daily (n = 227). *p < 0.001 vs. pentoxifylline (84).

dication. The results of these studies have been inconsistent. In a meta-analysis of five placebo-controlled trials, iloprost demonstrated a 21% increase in ulcer healing rates in patients with Fontaine stage 4 PAD compared with placebo (84). Furthermore, in another pooled analysis, patients with intermittent claudication who were randomized to receive oral prostanoids demonstrated a 30% improvement in mean maximum walking distance compared with subjects receiving the placebo (85). However, in a study by Mohler et al. (86) in which 897 patients with intermittent claudication were randomized to receive beraprost or placebo in a double-blinded manner for one year, there was no significant improvement in maximum walking distance in the beraprost group compared with the placebo group. Administration of beraprost did not improve the pain-free walking distance, and there was no improvement in the quality-of-life measures between the treatment groups. Therefore, prostaglandins cannot be recommended for the treatment of either claudication or CLI.

CLI. Critical limb ischemia is the precursor of limb loss and requires urgent treatment. Conservative management includes limited debridement of ulcers, the provision of appropriate footwear, use of non-adherent dressings, institution of adjunctive wound-healing techniques, and treatment of infection (unloading of the foot and administration of antibiotics). Surgical drainage and debridement are often required to resolve the infection, and revascularization is usually indicated (12). Indeed, revascularization is the preferred treatment in patients with CLI, as surgical debridement without revascularization tends to lead to larger non-healing wounds. Successful management of CLI requires not only treatment of the presenting symptoms (ulceration and infection), but also of the underlying ischemia.

Revascularization. Many patients may not experience optimal improvement in symptoms with medical therapy alone (82). Over recent years, revascularization has emerged as an important strategy for management of these patients. Two general revascularization techniques exist: endovascular interventions and open surgical procedures. Endovascular revascularization has increased in popularity in recent years; data available from the U.S. reveals a more than five-fold increase in endovascular interventions from 1980 to 2000 (87).

In general, endovascular revascularization is more appropriate in patients with relatively focal disease in arteries above the knee; however, short-term success rates for opening long totally occluded vessels and below-the-knee arteries are improving. To date, the best results have been achieved in the aortoiliac vessels, where one-year patency rates of 80% to 90% have been demonstrated (17,88).

In diabetes, open surgical revascularization tends to have greater durability than endovascular procedures. Bypass to the tibial or pedal vessels with autogenous vein is the most predictable method of improving blood flow to the threatened limb (12). Indeed, surgical bypass with greater saphenous vein is the procedure of choice for patients with diabetes and tibial disease.

Revascularization is the definitive therapy for the management of patients with CLI, with the aim of healing ischemic ulcers and preventing limb loss. Surgical revascularization is generally superior to endovascular procedures (3). Although most ischemic limbs can be revascularized, lack of a target vessel, unavailability of an autogenous vein, or irreversible gangrene may mean that some cannot. In these patients, amputation may be a better option than prolonged medical treatment (12).

Amputation. A careful program of medical and surgical interventions can prevent most limb amputations. However, amputation may represent an acceptable option for patients facing a prolonged course of treatment and a poor prognosis for a successful outcome. Amputation is indicated when there is overwhelming infection that threatens the patient's life, or when necrosis secondary to a major arterial occlusion has destroyed the foot.

CONCLUSIONS

Peripheral arterial disease is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is much higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in non-diabetic individuals. Moreover, the presence of PAD is a potent marker of increased cardiovascular risk. If PAD is identified on the basis of an ABI of <0.90, its prevalence in patients with diabetes may be as high as 29%.

Because the major threat to patients with diabetes and PAD is from cardiovascular events, the primary therapeutic goal is to modify atherosclerotic risk factors. Risk factor management includes lifestyle modifications, treating associated conditions (diabetes, dyslipidemia, and hypertension), and preventing ischemic events with aggressive antiplatelet therapy such as clopidogrel. Pharmacologic therapies to improve symptomatic PAD include cilostazol. A supervised exercise program or cilostazol are the preferred

first treatment steps for the management of symptomatic PAD. Revascularization has an important role to play in the management of patients for whom risk factor modification and pharmacological treatment prove inadequate.

The ADA consensus statement strongly recommends that cardiologists act cooperatively and effectively with other clinical specialists in order to reduce the atherothrombotic events that too often result in much of the death and disability in patients with diabetes and PAD.

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