Contemporary treatment for patients with peripheral artery disease (PAD) uses strategies to reduce the risk of adverse cardiovascular events, and preserve limb viability. Risk factor modification and antiplatelet drugs are the mainstay for secondary prevention of myocardial infarction (MI) and stroke in patients with PAD. Other than exercise training, there are woefully few interventional therapies that improve limbs symptoms or prevent amputation. This review will explore the evidence supporting recommendations for current medical treatment and discuss findings from recent studies that have therapeutic implications for patients with PAD. Unfortunately, indicated pharmacological treatments are greatly underutilized in PAD patients, especially in those patients without concomitant symptomatic coronary disease (Figure 1).

Management of a patient with PAD must first take into consideration that PAD is both a risk marker for systemic atherothrombotic events, as well as a distinct disease state with associated morbidity related specifically to atherosclerosis and thrombotic complications in the limb vasculature. Patients with PAD often have concomitant ischemic heart disease or cerebrovascular disease, and clinicians must take those disease states into account when determining an optimal treatment strategy. This is particularly the case with intensive antithrombotic therapy, which may have a heterogeneous risk-benefit profile, where intensive treatment with multiple

Abstract: Patients with peripheral artery disease (PAD) are at heightened risk of both systemic cardiovascular adverse events, as well as limb-related morbidity. The optimal management of patients with PAD requires a comprehensive treatment strategy incorporating both lifestyle changes, including smoking cessation and exercise, as well as optimal medical therapy. Pharmacological therapies for patients with PAD are targeted both at modifying broad risk factors for major adverse cardiovascular events, as well as reducing limb-related morbidity. Observational data suggest that indicated pharmacological treatments are greatly underutilized in PAD, underscoring the need for improvements in patient identification and care delivery. Ongoing trials of novel therapies in patients with PAD will further inform pharmacological strategies to reduce both systemic cardiovascular risk and limb-related morbidity. (Circ Res. 2015;116:1579-1598. DOI: 10.1161/CIRCRESAHA.114.303505.)

Key Words: medical therapy ■ peripheral artery disease
antithrombotic drugs may cause harm in patients with prior stroke and benefit in patients with prior MI.9-11

Also, rates of limb-related morbidity are significant in patients with symptomatic PAD. Indeed, the incidence of peripheral revascularization, acute limb ischemia (ALI), and amputation are equal to or exceed systemic atherothrombotic events, such as MI or stroke (Figure 2A and 2B).5,12 Moreover, these limb morbidities are associated with significant disability, and patients experiencing these events have high rates of repeat revascularization, hospitalization, and death.7,13-15

The second consideration for the clinician is that both the risk of major adverse cardiovascular events (MACE) and limb events, as well as the ability of therapies to reduce these risks, may be modified by whether the patient has symptomatic PAD.16-18 In general, the definition of symptomatic PAD is simply the presence of typical claudication symptoms in combination with an abnormal ankle:brachial index (ABI) or a history of a peripheral revascularization for ischemia.8,16 In contrast, asymptomatic PAD is defined as the finding of an abnormal ABI (<0.90) alone without limb symptoms or history of peripheral revascularization.5,16 In part, the distinction between symptomatic PAD and asymptomatic PAD reflects differences in trial populations and discordant outcomes with regard to therapy.16 Whether there are other pathobiological differences between symptomatic and asymptomatic PAD is uncertain; however, symptomatic patients have more severe disease, more comorbidities, and higher absolute risk of adverse cardiovascular events.7,16

The following review will be divided into 2 distinct sections, with one examining therapies for systemic vascular protection to reduce adverse cardiovascular events and the other focusing on therapies to reduce limb morbidity. Although this distinction is somewhat artificial given the systemic nature

<table>
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<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
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<tr>
<td>ABI ankle:brachial index</td>
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<td>ALI acute limb ischemia</td>
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<td>CAD coronary artery disease</td>
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<td>CLI critical limb ischemia</td>
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<tr>
<td>MACE major adverse cardiovascular events</td>
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<tr>
<td>OMC optimal medical care</td>
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<tr>
<td>PAD peripheral artery disease</td>
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<tr>
<td>PAR protease-activated receptor</td>
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<td>TIA transient ischemic attack</td>
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Figure 1. Utilization of preventive therapies in patients with peripheral artery disease (PAD*) and no other known cardiovascular disease, based on an ankle:brachial index (ABI) ≤ 0.90, from the National Health and Nutrition Examination Survey, 1999 to 2004. *Defined as patients with known history of PAD. ACEi indicates angiotensin-converting enzyme inhibitors; and ARB, angiotensin receptor blockers. Adapted from Pande et al. Circulation 2011. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Figure 2. A. Rates of systemic cardiovascular events, including myocardial infarction (MI) and stroke, and of limb ischemic events, including peripheral revascularization and amputation, in the REACH registry. *Defined as intermittent claudication with an ABI < 0.90 and a history of intermittent claudication along with prior peripheral revascularization or amputation. Adapted from Kumbhani et al.7 Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. B. Rates of systemic cardiovascular events, including myocardial infarction (MI) and stroke, and of limb ischemic events, including peripheral revascularization and amputation, in the TRA2P-TIMI50 study. *Defined as intermittent claudication with an ABI < 0.85 and a history of intermittent claudication along with prior peripheral revascularization or amputation. Adapted from Bonaca et al.12. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. ABI indicates ankle:brachial index.
of atherosclerotic vascular disease, it is necessary in order to evaluate existing data.

**Therapies to Reduce Systemic Cardiovascular Events**

The risk of MI, stroke, and death are increased in patients with atherosclerotic PAD, as discussed in detail elsewhere in this compendium.3 Risk factor modifying therapies and antiplatelet drugs are recommended in patients with PAD, as they are in patients with coronary artery disease (CAD) and cerebrovascular disease.16 Much of the evidence supporting the use of these therapies is derived from trials of broader populations of patients with atherosclerotic vascular disease, inclusive of PAD subgroups, and some comes from dedicated trials of PAD patients.

**Smoking Cessation**

The foundation of cardiovascular risk reduction in patients with any degree of PAD is lifestyle modification. Interventions focused on smoking cessation, dietary modification, and regular exercises are essential to the comprehensive care of patients with PAD. Successful lifestyle interventions not only have the potential to reduce the risk of adverse cardiovascular events, but also come with little risk of side effects and at relatively low cost relative to procedural interventions or long-term medical therapy.16

Smoking cessation warrants specific discussion because it has been described as the single most important modifiable risk factor for PAD.8,19 The importance of smoking cessation is underscored by its inclusion in professional guidelines as a performance measure for patients with PAD.20

In a cohort of 133 patients with symptomatic PAD, survival in patients who had ceased smoking was twice that of those who continued to smoke at 5 years.21 The relationship of smoking cessation and survival has shown mixed results in other cohorts. The Spanish Factores de Riesgo y ENfermedad Arterial Registry investigators described outcomes after a mean of 14 months in 3523 patients with stable vascular disease, inclusive of 1182 current smokers of which 467 had PAD, 475 had CAD, and 240 had cerebrovascular disease.22 Overall, they found smoking cessation was associated with a reduction in mortality during follow-up; however, the benefit appeared heterogenous by symptomatic vascular bed, with a significant reduction in those with CAD (adjusted hazard ratio [HR] 0.20, 95% confidence interval [CI] 0.05–0.75) and no significant effect in patients with PAD (adjusted HR 1.83, 95% CI 0.65–5.15). It should be noted that the relative number of deaths in patients with PAD was lower than in those with CAD, accounting for the broad confidence intervals.22 In addition, the duration of follow-up may have been too short to observe a benefit in terms of survival.

Although there are no prospective trials to demonstrate that smoking cessation results in improved outcomes in patients with PAD, the strength of the observational data support guideline recommendations that PAD patients receive comprehensive instruction, including behavior modification and consideration of pharmacological treatment.16

The effectiveness of smoking cessation programs in patients with PAD has been evaluated. One trial randomized 124 patients with PAD who were current smokers to either an intensive tailored PAD-specific counseling program or a minimal intervention and evaluated for smoking cessation.23 Patients were followed by surveys and cotinine or carbon monoxide measurement. The median number of sessions completed was 8.5 (range 0–18), with increased abstinence in the counseling intervention group at 6 months (21.3% versus 6.8%, P=0.023).23 It should be noted, however, that even with intensive counseling, almost 80% were no longer abstinent at 6 months, underscoring the need for additional therapies.

In addition to intensive counseling, there are pharmacological therapies to support smoking cessation. Beyond nicotine replacement, there is the norepinephrine and dopamine reuptake inhibitor, bupropion. When evaluated alone or in combination with a nicotine patch in a broad population of smokers, and compared with placebo or a nicotine patch alone, bupropion was found to result in significantly higher long-term (12 months) rates of smoking cessation than placebo or nicotine patch alone (15.6% with placebo, 16.4% with nicotine alone, 30.3% with bupropion alone, 35.5% with bupropion and nicotine).24 Rates of abstinence were highest with combination therapy with nicotine and bupropion; however, the difference with or without nicotine was not statistically significant.24

More recently, the partial nicotinic acetylcholine receptor agonist varenicline has been evaluated in smokers with stable cardiovascular disease. A total of 714 patients (179 with PAD) were randomized to varenicline 1 mg twice daily or matching placebo for 12 weeks along with counseling.25 At 12 weeks, abstinence rates were higher with varenicline compared with placebo (47% versus 13.9%) with the benefit consistent when evaluated for continuous abstinence from weeks 9 through 52 (19.2% versus 7.2%). The trial was conducted in part to show the safety of therapy in patients at high cardiovascular risk. Although treatment with varenicline was not associated with increased cardiovascular events, overall event rates were low, limiting definitive conclusions about safety.25

Clinicians treating patients with PAD should make smoking cessation a priority and use all of the modalities available, including counseling and pharmacotherapy.16 In spite of the available therapies, it should be noted that rates of abstinence at 1 year remain low (20% to 35%), underscoring the need for additional interventions targeting this modifiable risk factor.

**Smoking Cessation Summary**

All patients with PAD should be asked about tobacco use. Evaluation using the 5A algorithm may be useful (see Table).26 A combination of behavioral support and pharmacological therapy is likely to produce higher quit rates than either one alone. Some centers use contracts to formalize the intention to stop smoking. The most effective pharmacological therapies for smoking cessation include nicotine replacement, bupropion, and varenicline.26

Combination pharmacological therapy may be considered in patients who are unable to quit with individual therapies. One area of uncertainty remains in the use of e-cigarettes, where there is currently little literature to assess safety.27
The benefit of statin therapy in patients with symptomatic PAD was further explored in an analysis of 1404 patients with critical limb ischemia (CLI) undergoing lower extremity bypass. In this observational analysis, 1 year survival was greater in those using statins compared with those not using statins, which was consistent after propensity score adjustment (86% versus 81.4%; HR for death 0.71, 95% CI 0.52–0.98, \( P=0.03 \)).

A more recent study exploring statin use and adverse events in patients with CLI was a retrospective review of 380 patients with CLI who had undergone diagnostic angiography or endovascular intervention. After adjustment, statin therapy was associated with lower rates of systemic vascular events, including stroke, MI, or death (HR 0.53; 95% CI 0.28–0.99), with the greatest effect observed for mortality (HR 0.49; 95% CI 0.24–0.97).

Similar benefit with regard to MACE in patients with PAD was observed in a robustly sized subgroup of the REACH registry. A total of 5861 patients with documented PAD defined as current intermittent claudication and an ABI <0.90 and a history of intermittent claudication in addition to a history of peripheral vascular intervention were included. In addition, patients had to have complete follow-up information at 4 years to be included in the analysis subgroup. After multivariate adjustment, statin use was associated with a significant reduction in the composite of cardiovascular death, nonfatal MI, and stroke (HR 0.85, 95% CI 0.75–0.96, \( P=0.0071 \)) with symmetrical reduction in nonfatal MI and stroke.

The Heart Protection Study is the only large randomized study that included a group of patients with PAD. Heart Protection Study randomized 20536 patients to simvastatin 40 mg daily or placebo. Overall, simvastatin reduced the risk of major vascular events by 24% (19.8% versus 25.2%, \( P<0.0001 \)), including a reduction in all cause mortality (12.9% versus 14.7%, 18% relative risk reduction (RRR), \( P=0.0003 \)). The benefits in terms of vascular event reduction with simvastatin were consistent in the subgroup of patients with PAD (N=6748), regardless of whether they had a history of MI or other coronary heart disease (no coronary heart disease group, event rate ratio 0.75, 95% CI 0.67–0.84, \( P<0.0001 \)). Overall, there was a 22% relative reduction in the rate of first major vascular event with simvastatin versus placebo (26.4% versus 32.7%, \( P<0.0001 \)). In addition to benefit in terms of systemic events, there was a 16% reduction in peripheral vascular events with simvastatin versus placebo (4.7% versus 5.5%), with this benefit largely driven by a 20% relative reduction in noncoronary revascularization (3.3% versus 4.0%, \( P=0.002 \)). The reduction in peripheral events with simvastatin was independent of baseline LDL and other risk factors.

In 2007, available data reporting outcomes from randomized trials of lipid lowering, therapy, including subgroups of patients with PAD, was pooled in a Cochrane analysis. This included 18 trials and 10049 patients.

Trials differed considerably with regard to inclusion criteria and lipid lowering therapy. Overall, there was no benefit of lipid lowering in patients with PAD with regard to MACE. This was largely as a result of one trial showing a detrimental effect of lipid lowering therapy using cholestyramine. When excluding this trial, lipid lowering significantly reduced cardiovascular events (odds ratio 0.74, 95% CI 0.55–0.98); however, it should be noted that this result was largely driven by the Heart Protection Study results reviewed earlier.

The ACC (American College of Cardiology)/AHA (American Heart Association) PAD Guidelines recommend lipid lowering therapy with a statin for patients with PAD, targeting an LDL-cholesterol <100 mg/dL, and suggest that lower targets (<70 mg/dL) may be beneficial in high-risk patients. The recent ACC/AHA/CDC (Centers for Disease Control) cholesterol treatment guidelines focus on patient risk and intensity of statin therapy rather than lipid targets, noting that the majority of evidence showing cardiovascular risk reduction has been shown with statin therapy rather than other mechanisms of lipid lowering. Patients with PAD are included in the category of secondary prevention in which high-intensity statin therapy is recommended for all patients \(<75\) years. Patients >75 years and those unable to tolerate high-intensity statin therapy may be treated with moderate-intensity statin therapy. In patients unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, a nonstatin cholesterol-lowering drug may be considered.
Lipid Lowering Therapy Summary
Lipid lowering with statins has been shown to reduce the risk of MACE in patients with PAD and is recommended by current treatment guidelines. Ongoing trials will help to clarify the benefits of nonstatin lipid-lowering therapies in patients with PAD.

Antihypertensive Therapy
Hypertension is associated with adverse cardiovascular outcomes, and antihypertensive therapies reduce these risks.
Few studies of antihypertensive therapy have specifically included patients with PAD. The Appropriate Blood Pressure Control in Diabetes study enrolled 950 patients (480 normotensive and randomized them to either placebo (moderate blood pressure control) or treatment with enalapril or nisoldipine (intensive blood pressure control) and followed them for 5 years. A subgroup of 53 patients met the definition of PAD at baseline (ABI <0.90). In this subgroup, there were 3 cardiovascular events (13.6%) with intensive treatment and 12 events (38.7%) with moderate treatment (P=0.046). Although the number of events was small, the authors concluded that in PAD patients with diabetes mellitus, intensive blood pressure lowering to a mean of 128/75 mm Hg resulted in a marked reduction in cardiovascular events.

More recently, a post hoc analysis of the International Verapamil-SR/Trandolapril study examined whether treatment to a blood pressure <130/80 mm Hg was beneficial in patients with PAD. The trial included hypertensive patients with concomitant PAD and CAD with a total of 2699 PAD patients followed for a mean of 2.7 years. Overall, the rate of cardiovascular events was higher in patients with PAD compared with those without PAD (16.3% versus 9.2%). There appeared to be a J-shaped relationship between achieved blood pressure and outcome with the lowest event rates in those with a systolic pressure between 135 and 145 mm Hg and a diastolic pressure between 60 and 90 mm Hg. Interestingly, this J-shaped relationship was not observed for patients without PAD. The authors concluded that PAD patients may require a different target blood pressure relative to non-PAD patients.

Although there are few clear comparative studies evaluating whether specific antihypertensive therapies are beneficial, there are data supporting angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers. The benefits of ACEi therapy in particular were clearly shown by the Heart Outcomes Prevention Evaluation trial, which randomized 9297 patients with evidence of vascular disease or diabetes mellitus to ramipril 10 mg daily or placebo for 5 years. The Heart Outcomes Prevention Evaluation trial included 4051 patients withPAD, 44% of the overall cohort. Overall, ramipril significantly reduced the primary end point of cardiovascular death, MI, or stroke (14.0% versus 17.8%, relative risk 0.78, 95% CI 0.70–0.86, P<0.001).

There were significant reductions in the individual components of cardiovascular death (relative risk [RR] 0.74, P<0.001), MI (RR 0.80, P<0.001), and stroke (HR 0.68, P<0.001), as well as secondary end points of revascularization and cardiac arrest. This robust benefit was seen in the context of a relatively modest blood pressure lowering effect (5 mm Hg difference in mean systolic blood pressure at 1 month, decreasing to 3 mm Hg at study completion). The benefits of ramipril among the subgroup of patients with PAD were consistent with the overall trial.

The EUROPA trial randomized 12218 patients to either perindopril or placebo and followed them for a mean of 4.2 years. Treatment with perindopril resulted in a 20% reduction in the primary end point of cardiovascular death, MI, or cardiac arrest compared with placebo (P=0.0003). Approximately 7% of the population had PAD, with consistency in this subgroup with regard to the primary trial findings. The ON TARGET trial evaluated whether treatment with the angiotensin receptor blocker telmisartan was beneficial compared with ramipril alone, as well as the combination of both therapies, in over 25000 patients with vascular disease or with risk factors. Over 3000 patients (~13%) of the randomized population had PAD. Overall outcomes with telmisartan were equivalent to ramipril for the primary end point of cardiovascular death, MI, stroke, or hospitalization for heart failure (RR 1.01, 95% CI 0.94–1.09) with consistency in the PAD subgroup.

Combination therapy did not provide additional benefit and was associated with more adverse events compared with either monotherapy. Overall, these data support the use of ACEi and also angiotensin receptor blocker therapy in patients with vascular disease, including those with PAD.

Use of β-blockers is not recommended as first line therapy for patients with PAD; however, their use is not contraindicated. β-Blocker therapy can be used in patients with PAD and comorbid conditions, such as atrial fibrillation or CAD, for which use is indicated. The concept that β-receptor antagonism may worsen limb symptoms in patients with PAD is based on several potential mechanisms, including reduction of cardiac output, induction of reflex sympathetic activity, and an imbalance of α and β agonism in the peripheral vasculature, resulting in vasoconstriction and impaired peripheral perfusion. Early studies evaluating nonselective β-blockers in patients with severe PAD suggested worsening limb symptoms.

Subsequent studies, however, have not confirmed these effects. An early meta-analysis evaluated β-blocker use in patients with symptomatic PAD and found no effect on pain-free walking distance. More recent meta-analyses by the Cochrane Library included 6 randomized controlled trials and 119 patients. Overall, there was no evidence that β-blockers adversely impacted walking distance in patients with symptomatic PAD. Taken together, these data are reassuring; however, it should be noted that numbers available for inclusion (119 patients in the Cochrane study) are small, that there are no comparative trials between nonselective and β1 selective β blockers, and that there are no large prospective trials evaluating β-blockers and limb outcomes.

A study evaluating nebivolol, a third-generation β1 blocker with vasodilatory properties mediated through the l-arginine/nitric oxide pathway, and no intrinsic sympathomimetic activity, in patients with PAD was not included in the Cochrane systematic review.
A total of 177 patients with PAD and Fontaine stage II claudication were randomized to either nebivolol or hydrochlorothiazide and treated for 24 weeks. Overall, limb outcomes were similar between groups, leading the authors to conclude...
that nebivolol showed no negative effects in hypertensive patients with symptomatic PAD. Based on the lack of adverse effects observed in these studies, β-blockers are not contraindicated in patients with symptomatic PAD.

**Antihypertensive Therapy Summary**

In general, it is recommended that patients with PAD have blood pressure controlled to standard targets of ≤140/90 mmHg, as in most other patients with hypertension. Although dedicated trials of specific agents are lacking in patients with PAD, the overwhelming evidence overall supports benefit in treating hypertension. Data suggest that ACEi therapy may be of particular benefit. β-Blockers can be used safely in PAD patients who have an indication, such as CAD.

**Treatment of Diabetes Mellitus**

Treatment of diabetes mellitus in patients with established cardiovascular disease, including symptomatic PAD, is complex. Patients with diabetes mellitus are at increased risk for macrovascular complications, including MI, stroke, and cardiovascular death. In patients with PAD, diabetes mellitus is associated with endothelial dysfunction, vascular dysfunction, and impaired artery elastic properties. In addition, observational studies suggest that elevated fasting glucose is associated with lower vessel patency rates and increased rates of adverse limb events in diabetic patients undergoing peripheral angioplasty. Although the data associating diabetes mellitus to future adverse macrovascular events is robust, trials to demonstrate reduction in MACE with glucose lowering therapies have been largely neutral and some have suggested harm with intensive glucose lowering in patients with established cardiovascular disease.

Long-term follow-up data from the United Kingdom Prospective Diabetes Study, however, showed an emergent macrovascular benefit at 10 years, suggesting that cardiovascular risk reduction may only become apparent after long-term treatment. United Kingdom Prospective Diabetes Study randomized 4209 patients with newly diagnosed type II diabetes mellitus to dietary restriction or intensive therapy (sulfonylurea, insulin, or metformin).

At 5 years, intensive glucose therapy was associated with a reduction in microvascular complications, but not macrovascular complications. At 10-year follow-up (mean 8.8 years post-trial follow-up), the investigators found that the microvascular benefit was sustained and that there was an emergent reduction in MI (15% RRR, P=0.014) and all-cause mortality (RRR 6%, P=0.007). The benefit was seen in spite of no attempt to maintain previously assigned therapies in the extension and loss of glycemic difference.

The Action to Control Cardiovascular Risk in Diabetes trial investigated whether intensive glucose lowering therapy with a target of normal glycohemoglobin levels would reduce macrovascular events in patients with known cardiovascular disease, including PAD (35%) or risk factors. A total of 10,251 patients were randomized, with the intensive therapy group achieving a median glycohemoglobin level of 6.4% and standard therapy achieving 7.5%. After a mean of 3.5 years, a finding of higher mortality in the intensive treatment group led to a discontinuation of intensive therapy. Overall, intensive therapy reduced the risk of MI but did not significantly reduce the composite of MACE and increased both all-cause mortality, as well as cardiovascular mortality. The ADVANCE trial similarly showed no benefit of intensive glucose control on macrovascular outcomes. At a median of 5 years of follow up, the intensive group achieved a lower glycohemoglobin (6.5% versus 7.3%), but there was no reduction in major macrovascular events (HR 0.94, 95% CI 0.84–1.06, P=0.32). Unlike Action to Control Cardiovascular Risk in Diabetes, there was no increase in mortality with intensive therapy in ADVANCE (all-cause mortality HR 0.93, P=0.28), but there was more severe hypoglycemia (HR 1.86, P<0.001). A third trial examining intensive glucose lowering in patients with type II diabetes mellitus, including 40% of participants with cardiovascular disease, showed no reduction in macrovascular events at a median follow-up of 5.6 years.

The ORIGIN trial tested the hypothesis that increasing basal insulin in patients with impaired fasting glucose or type II diabetes mellitus would reduce cardiovascular events. A total of 12,527 patients, including 971 with an ABI ≤0.90, were randomized to receive either insulin glargine with a target fasting glucose of ≤95 mg/dL or standard care and were followed for a median of 6.2 years. There was no reduction in the composite of cardiovascular death, non-fatal stroke, or nonfatal MI with glargine. There was also no reduction in amputation (0.8% versus 0.8%, HR 0.89, 95% CI 0.60–1.31, P=0.55). There was, however, more hypoglycemia and weight gain with glargine. Although pharmacological interventions to lower plasma glucose have largely not shown benefit for cardiovascular risk reduction, the Look AHEAD investigators investigated whether glucose lowering through intensive lifestyle intervention would be beneficial.

A total of 5145 patients with diabetes mellitus were randomized to standard treatment and education or standard treatment with the addition of an intensive lifestyle intervention, with 714 having cardiovascular disease (including prior lower extremity revascularization). Over 10 years, the intensive lifestyle intervention was effective in reducing weight (−4 kg, P<0.001) and waist circumference (P<0.001), improving physical fitness (P<0.001), and reducing glycohemoglobin (−0.22, 95% CI −0.28 to −0.16, P<0.001). There was, however, no associated benefit in reduction in cardiovascular risk (HR 0.95, 95% CI 0.80–1.09, P=0.51), and there appeared to be heterogeneity (P interaction 0.06) with patients, with no cardiovascular disease having a trend toward benefit (HR 0.86, 95% CI 0.72–1.02), whereas those with established cardiovascular disease appeared to show a trend toward harm (HR 1.13, 95% CI 0.90–1.42). These data suggest that the optimal time for intensive intervention may be before the onset of symptomatic vascular disease.

Although glucose lowering alone has not shown benefit in patients with diabetes mellitus, the Steno-2 study evaluated an intensive intervention with multiple drug combinations and behavior modification patients with type II diabetes mellitus and microalbuminuria and showed sustained beneficial effects with respect to vascular complications and mortality.
Aspirin, antihypertensive therapy, and lipid lowering therapies each reduced the relative risk of cardiovascular events by ≈25%, with additive benefit. The overall treatment effect was largely driven by these therapies rather than glucose lowering, thus demonstrating that the risk of macrovascular events in patients with diabetes mellitus is modifiable.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PRO-active) trial randomized 5238 high-risk patients with diabetes mellitus to the peroxisome proliferator–activated receptor gamma agonist pioglitazone or placebo and followed them for a mean of 34.5 months. To qualify, patients had to have established atherosclerotic vascular disease, including 1043 patients qualifying with symptomatic PAD. Overall, there was no benefit with pioglitazone for the primary broad cardiovascular composite, which include MACE, revascularization, and amputation. There was benefit, however, in the secondary composite of cardiovascular death, MI, or stroke (0.84, 95% CI 0.72–0.98, P=0.027). Two additional studies evaluated the class of dipeptidyl peptidase 4 inhibitors in high-risk diabetic patients, including a majority with established atherosclerotic vascular disease, with the hypothesis that the use of a dipeptidyl peptidase 4 inhibitor may reduce cardiovascular risk beyond glucose lowering. Neither agent (saxagliptin or alogliptin) showed a reduction in macrovascular events in these high-risk populations, but both appeared to be safe in terms of ischemic risk.

Treatment of Diabetes Mellitus Summary

Although hyperglycemia is associated with incident symptomatic vascular disease, as well as macrovascular complications, in patients with established vascular disease, treatment to glucose targets has not been consistently shown to modify ischemic outcomes. Treatment is further complicated by trials that suggest potential harm with intensive glucose lowering treatment in patients with established cardiovascular disease.

Recent guideline statements have recommended a patient-centered approach recognizing the potential harms of hypoglycemia on cardiovascular health. Recommendations include latitude with more stringent glycemic targets for young patients with long life expectancy and no established vascular complications and less stringent targets for patients with established vascular disease.

Antithrombotic Therapy

Antiplatelet Therapy

The role of antiplatelet therapy for prevention in PAD is complex. This complexity is driven by the need to balance benefits in reduction in ischemic risk with risks of increased bleeding complications in the context of long-term preventive therapy. An overview of targets of antiplatelet agents is shown in Figure 3.

Early studies establishing benefit of antiplatelet therapy in patients with PAD are summarized in the Antithrombotic Trialists’ Collaboration Meta-analyses. An updated meta-analysis published in 2002 included 9214 patients with symptomatic PAD and overall showed a 23% reduction in the risk of serious vascular events defined as the composite of cardiovascular death, MI, or stroke with antiplatelet therapy. This benefit was consistent across PAD subgroups, including patients with intermittent claudication, peripheral grafting, and peripheral angioplasty. There was an associated risk of bleeding with the odds ratio for major extracranial bleeding of 1.6 (95% CI 1.4–1.8) with antiplatelet therapy. Although these data are broadly used as evidence of the efficacy of aspirin in prevention, it should be noted that the trial included studies evaluating several antiplatelet regimens, including different doses of aspirin, thienopyridines, dipyridamole, combination therapy, and picotamide. In fact, of the 9214 patients included in the analysis, 2304 were from a trial comparing the thromboxane synthase inhibitor, picotamide, to placebo in patients with PAD. The authors concluded that overall antiplatelet therapy was associated with a reduction in serious vascular events, that low-dose aspirin (75–150 mg daily)
was effective for long-term use, and that adding a second antiplatelet agent to aspirin might produce additional benefits, but that more research was needed to evaluate this strategy.\textsuperscript{66,67}

Although the benefit of antiplatelet therapy was established by earlier studies and the Antithrombotic Trialists meta-analyses, the role of aspirin specifically for cardiovascular protection in broader populations of patients with PAD was poorly defined. More recently, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial studied the efficacy of low dose aspirin (100 mg daily) in diabetic patients, without symptomatic cardiovascular disease, and PAD defined as an ABI $\leq 0.99$.\textsuperscript{69}

This study included 1276 patients who were randomized in a 2x2 factorial design to aspirin or placebo and antioxidant or placebo and followed for a median of 6.7 years accruing 8127 patient-years of follow-up.\textsuperscript{69} There was no benefit of aspirin for the primary composite primary end point of cardiovascular death, MI, stroke, or amputation for ischemia. Similarly, there was no benefit for the composite of coronary heart disease death or stroke or for any of the individual efficacy end points.\textsuperscript{69} The POPADAD trial was included along with other randomized controlled trials of aspirin therapy, without or with concomitant dipyridamole, in a subsequent metaanalysis of aspirin therapy in patients with PAD.\textsuperscript{18} The metaanalysis comprised a total of 5269 patients and included a subgroup of 3019 patients randomized to aspirin monotherapy or placebo. The aspirin dose varied from 100 mg daily to 1500 mg daily.\textsuperscript{18} There was no significant reduction in the primary composite end point of cardiovascular death/MI/stroke with aspirin compared with placebo (8.2% versus 9.6%, RR 0.75, 95% CI 0.48–1.18); however, the number of events overall was modest and lower with aspirin (125 events with aspirin versus 144 with placebo).\textsuperscript{18}

The Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index (AAA) trial further evaluated the role of aspirin in patients with PAD (defined as an ABI $\leq 0.95$), detected at a screening evaluation, but otherwise no established cardiovascular disease.\textsuperscript{17} A total of 28980 patients were screened with 3350 patients randomized to aspirin 100 mg daily or placebo. Patients were followed for a mean of 8.2 years and a total of 357 primary end points (cardiovascular death, MI, stroke, or revascularization) accrued.\textsuperscript{17} Overall, there was no benefit seen with aspirin for the primary end point, as well as the individual components and broader secondary end points. Aspirin therapy, however, was associated with an increased risk of bleeding (HR 1.71, 95% CI 0.99–2.97).\textsuperscript{17} Thiopyridines act through irreversible inhibition of the platelet P2Y\textsubscript{12} receptor, inhibiting platelet aggregation.\textsuperscript{70} This class of therapy was initially explored in patients with PAD in the Swedish Ticlopidine Multicenter Study, in which the first generation thiopyridine reduced major cardiovascular events in 687 patients with symptomatic PAD, however, with significant adverse events, including thrombotic thrombocytopenic purpura and neutropenia.\textsuperscript{71,72} The second generation thiopyridine, clopidogrel, is better tolerated than its predecessor ticlopidine\textsuperscript{73} and has been most broadly evaluated in the setting of stable atherosclerosis and PAD.

The primary trial establishing the benefit of clopidogrel monotherapy for cardiovascular ischemic protection in stable patients with PAD was the clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial, which randomized 19185 patients with stable atherosclerotic vascular disease (prior MI, prior ischemic stroke, or symptomatic PAD) to either clopidogrel 75 mg daily or aspirin 325 mg daily for a mean of 1.91 years.\textsuperscript{74} A total of 6452 patients met the criteria of symptomatic PAD defined as current symptoms of claudication and an ABI $\leq 0.85$ or a history of claudication and prior peripheral revascularization or amputation. Among the patients with PAD, 21% also had a history of MI and 6% had a history of ischemic stroke.\textsuperscript{74} In the overall cohort, clopidogrel was superior to aspirin, reducing the rate of the primary composite of vascular death, ischemic stroke, or MI (5.32% versus 5.83%, RRR 8.7%, $P=0.043$). The greatest RRR was seen in the PAD cohort (annualized rates, 3.71% with clopidogrel versus 4.86%, RRR 23.8%, $P=0.0028$) as compared with the MI or stroke cohorts.\textsuperscript{74}

Overall safety appeared similar; however, rates of gastrointestinal bleeding and intracranial hemorrhage were numerically lower with clopidogrel compared with aspirin (gastrointestinal bleeding 1.99% versus 2.66%, intracranial hemorrhage [ICH] 0.35% versus 0.49%).\textsuperscript{74}

The CAPRIE results established the benefit of clopidogrel as monotherapy for cardiovascular protection in patients with symptomatic PAD and have been used as the basis for guideline recommendations recommending clopidogrel monotherapy in this population.\textsuperscript{16} Whether the benefits of clopidogrel can be extrapolated to later generation more potent thiopyridines or to the broader class of adenosine diphosphate (ADP) receptor blockers is unknown.

As data emerged supporting the benefit of dual antiplatelet therapy with aspirin and a thiopyridine in high-risk patients in the setting of acute coronary syndrome, it was hypothesized that this benefit might be seen in broader populations with stable atherosclerosis.\textsuperscript{75} The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial examined this hypothesis by randomizing 15603 patients with either established stable atherosclerotic vascular disease (coronary disease, cerebrovascular disease, or PAD) or multiple atherothrombotic risk factors to clopidogrel 75 mg daily in addition to low dose aspirin (75 mg–162 mg daily) or low dose aspirin monotherapy.\textsuperscript{76} Overall, the combination of aspirin and clopidogrel was not superior to aspirin monotherapy for the primary end point of death, MI, or stroke (6.8% versus 7.3%, $P=0.22$).\textsuperscript{76}

Subsequent exploratory analyses of a subgroup of 9478 patients in the CHARISMA trial with history of MI, stroke, or symptomatic PAD suggested that dual antiplatelet therapy with aspirin and clopidogrel may be beneficial (7.3% versus 8.8%, HR 0.83, 95% CI 0.72–0.96, $P=0.01$).\textsuperscript{77} Of the 2838 patients with symptomatic PAD, there was a numerically consistent but not statistically significant reduction in cardiovascular events with dual antiplatelet therapy versus aspirin monotherapy (7.6% versus 8.7%, HR 0.87, 95% CI 0.671–1.125, $P=0.29$).\textsuperscript{77} The CHARISMA authors also reported a subgroup analysis of cardiovascular outcomes in 2838 patients with symptomatic PAD and 258 patients with asymptomatic
PAD. In this subgroup, dual antiplatelet therapy did not reduce the primary end point of death, MI, or stroke (7, but was associated with lower rates of MI and hospitalization for ischemic events.78

In CHARISMA, overall there was an increase in bleeding with dual antiplatelet therapy relative to aspirin monotherapy, with a trend toward more severe bleeding (1.7% versus 1.3%, HR 1.25, 95% CI 0.97–1.61, P=0.09) and statistically significantly more moderate and minor bleeding.76,78,79

Protease-Activated Receptor-1 Antagonists

In addition to its role in the coagulation cascade, thrombin is a potent activator of platelets.80–82 In total, 4 protease-activated receptors (PARs) are known in mouse and human biology.83 PAR-1 and PAR-4 are activated by thrombin, whereas PAR-2 is activated by trypsin.82,83 PAR-3 is believed to function as a coreceptor for PAR-4, facilitating cleavage and activation of PAR-4 in mice. PAR-1 is present on platelets, endothelial cells, and smooth muscle cells. Human platelets express PAR-1 and PAR-4, with PAR-1 the predominant thrombin receptor on platelets in humans and PAR-4 likely providing some redundancy.

Thrombin binds to and subsequently irreversibly cleaves the amino terminus of the extracellular loop of the PAR-1 receptor at Arg41-Ser42.82,84 The new amino terminus becomes a tethered ligand that undergoes a conformational change, folding back over the receptor to auto-activate the transmembrane protein. Activation of the receptor initiates G-protein-coupled processes, including those mediated through Gq and Gi, which leads to -subunits bind Rho guanine-nucleotide exchange factors, as well as through Gq and Gi, which leads to increased intracellular Ca2+ and decreased cAMP.81,82,84

The downstream results of PAR-1 activation by thrombin on the platelet include changes in the ligand-binding properties of the glycoprotein IIb/IIIa receptor, allowing it to bind soluble adhesive proteins, such as fibrinogen and von Willebrand factor, furthering stabilizing platelet aggregation, as well as release of additional activators, including ADP, serotonin, and thromboxane A2.84 A new class of antiplatelet therapy that antagonizes the G-protein-coupled PARs has recently undergone clinical investigation.85,86

TRA2P-TIMI (Thrombin Receptor Antagonist for Secondary Prevention-TIMI Study Group) 50 trial assessed the efficacy of the PAR-1 antagonist, vorapaxar, on cardiovascular risk in stable patients with atherosclerotic vascular disease.86 The study randomized 26,449 patients with either history of MI, history of ischemic stroke, or symptomatic PAD to either vorapaxar 2.5 mg daily or matching placebo, in addition to background antiplatelet therapy, and followed patients for a median of 30 months.86

Overall, vorapaxar significantly reduced the primary end point of cardiovascular death, MI, or stroke compared with placebo (9.3% versus 10.5%, HR 0.87, 95% CI 0.80–0.94, P<0.001); however, qualitatively there appeared to be heterogeneity in the benefit according to symptomatic vascular bed. In particular, there was no significant benefit and increased risk of intracranial hemorrhage in patients with a history of stroke, prompting action by the data safety monitoring board to terminate the study early in that population.86

When excluding patients with stroke or transient ischemic attack (TIA), the remaining cohort of 20,170 with history of MI or symptomatic PAD had a consistent benefit in the reduction of MACE, including cardiovascular death/MI/stroke (10.4% versus 11.8%, HR 0.83, 95% CI 0.76–0.90, P<0.001) with no significant heterogeneity in benefit between patients with history of MI (N=16,856) or those with symptomatic PAD (N=3,252).87 At 3 years, vorapaxar increased the risk of moderate bleeding, but not severe or fatal bleeding. These results led to approval of vorapaxar by the US Food and drug administration for use as chronic therapy for the reduction of cardiovascular risk in patients with history of MI or symptomatic PAD and no history of stroke or TIA.87

Anticoagulants

The efficacy of anticoagulant compared with antiplatelet therapy on cardiovascular adverse events in patients with PAD was explored in 2161 patients with PAD in the Warfarin Antiplatelet Vascular Evaluation trial.88 Overall, the strategy of systemic anticoagulation with a vitamin K antagonist did not reduce cardiovascular events, but significantly increased the risk of life-threatening bleeding compared with antiplatelet monotherapy (RR 3.41, P<0.001).88

Antithrombotic Therapy Summary

Patients with PAD have a high risk of atherothrombotic events. Antithrombotic therapy, and particularly antiplatelet monotherapy, has shown benefit for atherothrombotic risk reduction in patients with symptomatic PAD.16 Symptomatic patients with an ABI ≤0.85 benefit from monotherapy with aspirin or clopidogrel, and there is some data suggesting that dual antiplatelet therapy with both drugs may be effective. Vorapaxar in combination with either aspirin, clopidogrel, or both reduces cardiovascular events in PAD patients who have no prior history of stroke or TIA, but is contraindicated if a history of stroke or TIA is present. The use of warfarin in preference to antiplatelet therapy is not recommended unless another indication is present, such as atrial fibrillation or mechanical prosthetic heart valve and has been associated with high rates of bleeding.16

The 2011 ACCF (American College of Cardiology)/AHA PAD guideline update states that antiplatelet therapy, including aspirin or clopidogrel, is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic lower extremity PAD and can be useful in asymptomatic patients with an ABI ≤0.90.16

The usefulness of antiplatelet therapy in asymptomatic individuals with borderline abnormal ABI, defined as 0.91 to 0.99, is not well established.16

Future Studies With Antithrombotic Drugs

Novel antithrombotic strategies for patients with PAD is an active area of research. The effect of the non-thienopyridine ADP receptor blocker, ticagrelor, as monotherapy, compared with clopidogrel on cardiovascular death, MI, or stroke, is undergoing study in >12,000 patients with symptomatic PAD in the Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease trial with results expected in 2016.89

The emergence of novel oral anticoagulants acting at specific targets in the coagulation cascade with more favorable
safety profiles than the vitamin K antagonists has raised the possibility that anticoagulation with a novel oral factor Xa inhibitor reduce ischemic risk with acceptable bleeding risk in patients with atherosclerotic vascular disease. The COMPASS trial is evaluating low dose rivaroxaban 2.5 mg, a dose shown to be effective in the setting of acute coronary syndrome, compared to placebo, in a broad population of over 20,000 patients with history of MI or symptomatic PAD.90

The ePAD trial is evaluating the Xa inhibitor edoxaban at standard dosing (60 mg once daily) in addition to aspirin 100 mg daily compared with clopidogrel 75 mg daily and aspirin 100 mg daily after intervention in patients with PAD and is estimated to enroll 200 patients.91

**Therapies to Reduce Limb Morbidity**

Limb-related morbidity refers to the symptoms and direct consequences of compromised blood flow to the leg. These include intermittent claudication, impaired walking function, pain, skin necrosis, and threatened limb viability resulting from acute limb ischemia (ALI) and chronic critical limb ischemia (CLI), the need for peripheral revascularization, and amputation. The risk of limb-related morbidity is significant in patients with symptomatic PAD (Figure 2A and 2B).5,12 Patients experiencing these events have high rates of complications, including repeat revascularization, hospitalization, and death.7,14,15

**Exercise Training**

The most effective noninvasive intervention for improving symptoms of claudication is exercise. Understanding the causes of leg claudication and impaired walking capacity in PAD may shed light on the mechanisms underlying the beneficial effects of exercise. Although limb symptoms are associated with diminished blood flow as measured by ABI, the association between ABI and walking distance is unclear.92 Other measures of blood flow, such as MRI-based techniques, similarly show modest associations with walking functional capacity. These data suggest that the functional limitation in...
patients with PAD is more complex than luminal obstruction. This complexity is further illustrated by the results with exercise training, which has been shown to significantly improve walking time, but has not been convincingly shown to lead to clinically relevant improvements in peripheral blood flow.

Although luminal narrowing clearly contributes to functional limitation, a growing body of data supports important contributions by cellular changes in the vasculature, as well as the skeletal muscle. Several studies have shown impaired endothelial vasodilator responses in PAD, including in the brachial arteries, demonstrating a systemic dysfunction rather than solely a local phenomenon. Changes to skeletal muscle seem to occur in the extremities affected by PAD and include both changes in overall mass and density, as well as cellular changes in energetics and metabolism. Mitochondrial dysfunction may lead to generation of reactive oxygen species, leading to inflammation and accelerated cellular damage (Figure 4). Exercise training has been shown to have several potential mechanisms of benefit addressing local and systemic derangements implicated in functional impairment.

These include upregulation of angiogenic growth factors and collateral blood vessel development; increased expression and activity of eNOS, and enhanced endothelium-dependent vasodilation; improved skeletal muscle metabolic function via increased muscle mitochondrial content and enzymatic activity; and better walking biomechanics (Figure 4). Improved muscle metabolism and energetics through alterations in mitochondrial function, coupled with better endothelial function and reduced blood cell viscosity, results in augmented oxygen delivery. Systemic changes, including reduction in inflammatory markers, also have been observed, indicating broad systemic benefits beyond walking capacity alone.

Individual studies and meta-analyses have found that supervised exercise training increases maximal walking time by 120% to 150% (Figure 5). Based on these data, the current ACC/AHA and the ESC (European Society of Cardiology) guidelines recommended supervised exercise for patients with PAD, with sessions occurring at least 3 times per week with exercise regularly once the program is completed. Exercise is also recommended in the ACC/AHA performance measures for patients with PAD.

Although less effective than structured exercise, home-based exercise programs should be recommended if supervised exercise is not available. A home-based walking exercise program integrating group-mediated cognitive behavioral intervention was evaluated in a randomized trial of 194 patients with PAD (Figure 5). Participants were randomized to home-based group-mediated walking or an attention control condition. At 6 months, the home-based intervention resulted in a significantly increased 6-minute walk distance (357.4–399.8 versus 353.3–342.2, mean difference 53.5, 95% CI 33.2–73.8, P<0.001), as well as significantly increased maximal walking time, physical activity, and Walking Impairment Questionnaire score. The results supported the benefit of home-based exercise in patients with PAD who are unwilling or unable to participate in supervised exercise. When evaluated again at 12 months, there was continued benefit of the home-based exercise intervention.

The efficacy of supervised exercise training compared with endovascular revascularization as an initial treatment strategy of patients with claudication and aortoiliac disease was evaluated in the CLEVER study. A total of 111 patients with aortoiliac disease were randomized to optimal medical care (OMC), OMC plus supervised exercise, or OMC plus stent revascularization. The primary end point was the change in peak walking time on a graded treadmill at 6 months with secondary end points exploring activity and quality of life. Overall, supervised exercise showed the greatest improvement in the primary end point (mean change from baseline 5.8±4.6 minutes, P=0.04 versus stenting and <0.001 versus OMC) followed by stenting (3.7±4.9), with the least benefit in those randomized to OMC only (1.2±2.6). Patient reported quality of life, however, was higher with stenting as compared with supervised exercise.

The question of whether supervised exercise training in addition to endovascular revascularization improves walking distance compared with supervised exercise alone was asked by the Revascularization and Supervised Exercise trial. A total of 212 patients with PAD (>50% aortoiliac and femoropopliteal) and intermittent claudication were randomized to either supervised exercise and stenting or supervised exercise alone. The combination of stenting and supervised exercise was superior to supervised exercise alone for maximum walking distance at 1 month (566 m mean difference, 95% CI 358–774, P<0.001) 6 months (409 m mean difference, 95% CI 183–436, P<0.001), and 12 months (282 m mean difference, 95% CI 60–505, P=0.001) with consistent increases in pain-free walking distance, ABI, and quality of life.

Of note, the supervised exercise intervention decreased in intensity during follow-up with 2 to 3 sessions per week in the first 3 months, 1 session per week at months 4 to 6, and 1 session per month during the last 3 months of follow-up.

Exercise Training Summary

Although the mechanisms are complex and continue to be elucidated, exercise training has multiple benefits in patients with PAD, including the reduction of limb symptoms, improvement in functional capacity, and the reduction of systemic cardiovascular risk. Exercise should be recommended for all patients with PAD with the exception of those with contraindications, including foot ulcers and or rest limb pain awaiting revascularization.

Smoking Cessation

Observational studies have shown an association between smoking cessation and reduction in incident claudication, improvements in ankle pressure and exercise tolerance, outcomes after revascularization, and survival in patients with PAD. In the Women’s Health Study, smoking cessation markedly decreased the risk for developing symptomatic PAD (Figure 6). The prospective Reykjavik Study showed a sharp decrease in the prevalence and incidence of intermittent claudication, with about one half of the decline explained by reductions in smoking and cholesterol. Functional assessment of patients with PAD and claudication has shown that smoking cessation is associated with improvement in ankle pressure and exercise tolerance, as well as reductions in limb vascular events, including CLI and amputation.
A recent analysis of 16,534 patients undergoing infragenual bypass showed an independent association between active smoking and early graft failure (adjusted odds ratio, 1.21; 95% confidence interval, 1.02–1.43; \( P=0.03 \)). Therefore, smoking cessation is considered a critical element in reducing limb morbidity.

**Antiplatelet Therapy**

Although aspirin showed benefit for prevention of systemic atherothrombotic events in the Antithrombotic Trialists Collaborative meta-analysis, there was no information regarding benefit for ALI or amputation.\(^{86,87}\) The POPADAD trial, described earlier, randomized patients with asymptomatic PAD to aspirin or placebo and showed no difference in the development of CLI (HR 1.11, 95% CI 0.60–2.06, \( P=0.75 \)) or above ankle amputation for CLI (HR 1.23, 95% CI 0.51–2.97, \( P=0.64 \)).\(^{69}\)

Similarly, the AAA study, which randomized asymptomatic patients with PAD to aspirin or placebo, showed no benefit for aspirin for future risk of claudication or peripheral revascularization.\(^{17}\)

The CAPRIE trial which randomized patients to either aspirin or clopidogrel did not report the end point of ALI; however, there were numerically more amputations with clopidogrel relative to aspirin (52 versus 47).\(^{74}\) In the PAD subgroup of the CHARISMA trial, there was a reduction in investigator-reported hospitalization with dual antiplatelet therapy with aspirin and clopidogrel compared with aspirin alone (16.5% versus 20.1%, HR 0.81, 95% CI 0.68–0.95, \( P=0.011 \)); however, the reasons are not provided and acute limb vascular end points were not reported.\(^{78}\)

The findings of CHARISMA, however, raise the possibility that more intensive antiplatelet therapy may be beneficial in preventing limb vascular events. The efficacy of dual antiplatelet therapy on limb events was assessed in the CASPAR trial, which was a randomized placebo controlled trial comparing aspirin 75 to 100 mg as monotherapy to therapy with aspirin and clopidogrel in patients undergoing peripheral bypass surgery.\(^{106}\) A total of 851 patients were randomized and followed for a maximum of 24 months. Overall, there was no benefit of dual antiplatelet therapy as compared with aspirin monotherapy with regard to the primary end point (graft occlusion, revascularization, or amputation; death; HR 0.98, 95% CI 0.78–1.23), graft occlusions (HR 0.94, 95% CI 0.71–1.25), or amputation (0.68, 95% CI 0.43–1.08).\(^{106}\)

The authors performed a sensitivity analysis restricted to only patients who continued on therapy through the trial and found results to be unchanged.\(^{106}\) As an exploratory analysis, the authors examined different graft types and found no benefit of dual antiplatelet therapy for venous grafts, but an associated reduction in graft occlusion in patients with prosthetic grafts.\(^{106}\) A trial called The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization or CAMPER study was designed to further explore the potential benefit of dual antiplatelet therapy after peripheral stenting. Because of poor enrollment, this study was terminated early.

In the TRA2P-TIMI 50 trial evaluating vorapaxar compared with placebo, the end point of hospitalization for ALI was prospectively defined and limb ischemic events were prospectively adjudicated.\(^{11}\) In the PAD subgroup, there was a significant 42% reduction in hospitalization for ALI with vorapaxar (2.3% versus 3.9%, HR 0.58, 95% CI 0.39–0.86, \( P=0.006 \); Figure 7).\(^{12}\) In addition, there was a consistent 35% reduction in urgent peripheral revascularization (HR 0.65, 95% CI 0.46–0.91) and a 28% reduction in urgent vascular hospitalizations (5.8% versus 8.0%, 95% CI 0.72, 95% CI 0.56–0.93, \( P=0.011 \)).\(^{12}\) These benefits were seen on top of antiplatelet therapy (97%), including 27% of patients of dual antiplatelet therapy with aspirin and clopidogrel, as well as on a background of statin therapy (82%). Vorapaxar did increase moderate or severe bleeding, including in the subgroup without stroke or TIA.\(^{12}\) Rates of ICH were numerically increased with vorapaxar (8 versus 5, HR 1.66, 95% CI 0.54–5.08, \( P=0.37 \)), and there was no difference in fatal bleeding (7 with vorapaxar versus 7 with placebo).

The reduction in ALI and urgent revascularization appeared early and conceptually was consistent with an antithrombotic effect in the limbs. There was, however, also a 14% reduction in site-reported elective peripheral revascularization (16.5% versus 19.5%, HR 0.86, 95% CI 0.74–0.9995, \( P=0.049 \)) with vorapaxar (Figure 7). Interestingly the Kaplan–Meier curves show separation for this endpoint beginning late after randomization, leading some to hypothesize that this reduction may be mediated through effects of PAR-1 inhibition on other issues.\(^{12}\) Indeed, animal models have shown arterial restenosis after balloon-mediated injury is reduced in the setting of PAR-1 antagonists.\(^{107}\) Whether this reduction in elective peripheral revascularization was driven by improvement in symptoms of claudication is not known.

**Anticoagulants**

The Warfarin Antiplatelet Vascular Evaluation Trial randomly assigned 2,161 patients with PAD to warfarin with an international normalized ratio target of 2 to 3 or antiplatelet therapy.\(^{38}\) At 35 months follow-up, there was no difference in peripheral severe ischemia between groups (3.9% with warfarin versus 4.1% with antiplatelet therapy, HR 0.96, 95% CI 0.63–1.47, \( P=0.86 \)). However, there was
a significant increase in life-threatening bleeding (4.0% with warfarin versus 1.2%, HR 3.41, 95% CI 1.84–6.35, P<0.001). Ongoing trials will help define whether newer generation anticoagulants targeting specific pathways have a role in reducing acute limb events.

**Cilostazol**

Cilostazol is a quinolone derivative that is a specific inhibitor of phosphodiesterase-3, which is reported to have a broad range of potentially beneficial actions, including reducing platelet aggregation and smooth muscle proliferation, as well as enhancing vasodilation. Although any of these mechanisms may lead to symptom benefit in patients with claudication, the exact mechanism is unknown. Several trials have shown that cilostazol improves symptoms of claudication in patients with PAD, with one showing a 35% increase in initial claudication distance and a 41% increase in absolute claudication distance. A meta-analysis published in 2002 included 2702 patients with stable moderate to severe claudication symptoms by reducing blood viscosity through increasing deformability of erythrocytes and leukocytes. The theophylline derivative, pentoxifylline, may improve claudication symptoms for claudication in patients with PAD included 7 randomized trials and found that there was a weighted mean difference in initial claudication distance of 31.1 m (95% CI 21.3–40.9) with cilostazol 100 mg twice daily compared with placebo.

A more recent meta-analysis included pooled original data from 9 randomized controlled trials evaluating cilostazol for intermittent claudication. A total of 1258 patients were treated with cilostazol 100 mg BID. Overall, cilostazol improved maximal walking distance by 50.7% compared with a 24.3% improvement with placebo and an absolute increase of 42.1 m over placebo (P<0.001).

One trial compared the efficacy of cilostazol with the methylxanthine derivative pentoxifylline. A total of 922 patients were randomized to either cilostazol 100 mg twice daily, pentoxifylline 400 mg 3 times daily, or placebo. Overall, mean maximal walking distance was significantly greater with cilostazol than with pentoxifylline or placebo. At 24 weeks of treatment, cilostazol resulted in a mean 54% increase from baseline compared with a 30% increase with pentoxifylline and a 34% increase with placebo, with no significant difference between pentoxifylline and placebo (P=0.82). Side effects (headache, palpitations, diarrhea) were more common with cilostazol, but there was no difference in treatment cessation between the 2 active groups. One large trial found no increase in all-cause or cardiovascular mortality with cilostazol.

However, because of its pharmacological similarity to milrinone and the associated harm observed with milrinone in patients with advanced heart failure, cilostazol should not be used in patients with heart failure or a reduced left ventricular ejection fraction (<40%). Although otherwise considered to be safe, cilostazol does have side effects, including diarrhea, headache, and dizziness, and therefore treatment durability may be an issue.

**Pentoxifylline**

The theophylline derivative, pentoxifylline, may improve claudication symptoms by reducing blood viscosity through increasing deformability of erythrocytes and leukocytes. Although pentoxifylline has been shown to improve symptoms of claudication, the overall benefit is small. Statins may also reduce oxidant stress and suppress inflammation. Smaller open label trials...
evaluating intensity of statin therapy and benefits in terms of flow-mediated dilation, intima-media thickness, or change in ABI have shown neutral results when comparing more intensive statin therapy to moderate intensity statin therapy. One study evaluated the efficacy of statins on hemorheologic variables in 100 patients with PAD randomized to either atorvastatin 80 mg daily or low intensity statin. Overall, there was no difference in plasma viscosity, red cell aggregation, whole blood viscosity, hematocrit, leukocytes, or the other parameters measured.

Several trials have shown potential benefits of statin treatment in patients with intermittent claudication. One randomized, double-blind, parallel-design study randomized 354 patients with PAD placebo, atorvastatin 10 mg daily, or atorvastatin 80 mg daily. At 12 months, there was a trend, but no significant difference in maximal walking time; however, there was significant improvement in pain-free walking time with atorvastatin 80 mg as compared with placebo. A second open label study found benefit in exercise time with simvastatin compared with placebo, with an increased onset of claudication by 54 seconds at 6 months and 95 seconds at 1 year with simvastatin compared with placebo. A third study randomized 86 patients with PAD and intermittent claudication to either simvastatin 40 mg daily or placebo and found an increase in mean pain-free walking distance of 90 m (95% CI 64–116, P<0.005) with simvastatin. In addition, there were improvements in total walking distance, ABI at rest and after exercise, and claudication symptoms with statin compared with placebo. A comprehensive review of therapies to improve walking capacity and improve symptoms of claudication in patients with PAD included 43 trials evaluating vasodilators, phosphodiesterase inhibitors, and lipid-lowering agents. Overall, lipid-lowering therapies showed the greatest benefit, with mean increase in maximal walking distance of 160 m, whereas the other agents only showed modest improvement (50 m) from baseline.

Statin use has also been associated with attenuation in functional decline. One study enrolled 323 patients with PAD and evaluated functional outcomes at 3 years. Treatment with statin was not randomized; however, after adjustment, statin use was associated with less annual decline in lower-extremity performance measured by walking velocity, 6-minute walk, and rapid-pace walking velocity in patients with PAD.

In addition to intermittent claudication, the efficacy of statins on other limb-related outcomes has been studied. The REACH investigators performed an exploratory analysis to assess the effect of statin therapy on limb outcomes. Among 5861 patients with symptomatic PAD, 62.2% were using statin therapy at baseline. After adjustment for differences, statin therapy was associated with a reduction in the composite of worsening claudication or CLI (HR 0.82, 95% CI 0.70–0.95, P=0.0087), as well as the risk of a new revascularization procedure (HR 0.83, 95% CI 0.72–0.95, P=0.0079; Figure 8).

In addition, the investigators found a significant reduction in new amputation (HR 0.64, 95% CI 0.48–0.86, P=0.0027). Although the comparison was nonrandomized, the analyses were adjusted for potential confounders and were consistent through a series of sensitivity analyses.

The Heart Protection Study which included 6748 patients with PAD (see section on lipid lowering) showed a 16% reduction in the rate of first acute peripheral vascular events with simvastatin compared with placebo (4.7% versus 5.5%, P=0.002), which was irrespective of baseline LDL cholesterol or other clinical factors. In a smaller retrospective analysis of 380 patients with CLI, statin use was associated with improved lesion patency among patients undergoing infrapopliteal angioplasty; however, there was no difference in lower extremity bypass (18% versus 18%, P=0.9). In this study, there was a numeric nonsignificant reduction in amputation (12% with statin versus 18% without statin, adjusted HR 0.68, 95% CI 0.32–1.39, P=0.30).

The benefits of statins on limb events was not seen in PREVENT-III, which evaluated 1404 patients with CLI undergoing lower extremity bypass (described earlier), in which there was no benefit of statin therapy on either primary patency (P=0.66) or secondary patency (P=0.80) at 1 year. Another observational analysis evaluated 717 patients undergoing revascularization for intermittent claudication or CLI of whom 55.4% were on statins. After adjustment, statin therapy was associated with increased survival; however, there was no associated benefit of statin therapy on long-term vessel patency or limb salvage.

Although individual trials show varied results, the overall data suggest a beneficial effect of lipid-lowering therapy, and in particular statin therapy, for limb outcomes, including worsening claudication, walking time, and limb vascular events of CLI, ALI, and amputation. Although high-intensity statin therapy is already indicated in symptomatic PAD patients, these findings may play a role in understanding the broad importance of widespread use and compliance in patients with PAD.

**Angiotensin-Converting Enzyme Inhibitors**

Broad potential vascular benefits have been described as possible mechanisms of benefit for ACEi therapy, beyond blood pressure lowering alone. These mechanisms include enhancement in endothelial function, reductions in oxidative stress, and other vascular protective effects. Several studies have evaluated the ability of ACEi therapy to modify claudication in symptomatic PAD.

The strongest data seem to be for ramipril, which was evaluated in a randomized double-blind placebo-controlled trial enrolled 212 patients with PAD and claudication to either ramipril 10 mg daily or matching placebo. At 6 months, ramipril treatment was associated with a 75 second (95% CI 60–89) increase in mean pain-free walking time relative to placebo (P<0.001). Ramipril also significantly improved the Walking Impairment Questionnaire score, stair climbing score, and Physical Component of the SF-36 Health Survey. Another study, however, which selected patients with PAD over the age of 65, did not find benefit of ACEi therapy.

A total of 170 patients were randomized to either perindopril 4 mg daily or matching placebo and all received progressive exercise training. At 20 weeks, both treatment groups
increased their walking distance (29.6 m with perindopril versus 36.4 m with placebo, \( P = 0.43 \)). Similarly, there was no difference between groups for the secondary outcomes of quality of life, functional impairment, or handgrip and quadriiceps strength. A meta-analysis of ACEi therapy in patients with PAD and claudication included 6 randomized controlled trials, including 821 patients. Overall, there was an increase in maximum walking distance (mean differences 120.8 m, 95% CI 2.95–238.68, \( P = 0.04 \)), improved pain-free walking distance (\( P = 0.003 \)), but no change in ABI (\( P = 0.11 \)). Benefit was largely driven by results with ramipril. Overall, it is not established that ACEi therapy modifies limb symptoms, and additional studies are needed; however, as with statins, it is beneficial for the reduction of MACE in patients with PAD and hypertension and, therefore, indicated in the majority of PAD patients.

**Summary and Conclusions**

Patients with PAD represent a distinct group of patients with atherosclerotic vascular disease. They are at increased risk of systemic ischemic events, associated with comorbid CAD or cerebrovascular disease. Symptomatic PAD patients also suffer significantly from limb-related morbidity. In high-risk patients with symptomatic PAD, \( \approx 1 \) in 4 will require a peripheral intervention over the next 3 to 4 years, and the rates of ALI and amputation are similar to the rates of stroke and MI. These high-risk patients are as likely or more likely to suffer limb-related morbidity as they are to suffer acute systemic ischemic events.

**Therapies for MACE Reduction**
- Lifestyle Modification
- Tobacco Cessation Therapies
- Statin therapy
- Blood Pressure control (ACEi or ARB preferred)
- Antiplatelet monotherapy may be beneficial in selected patients

**Therapies for Limb Vascular Event Risk Reduction**
- Statin therapy may be beneficial
- PAR-1 Antagonist for selected patients

**Therapies for Symptom Improvement**
- Exercise
- Cilostazol
- Statin therapy may be beneficial
- Revascularization

**Figure 8.** Effect of statin treatment on limb vascular events, including peripheral revascularization and amputation in patients, with symptomatic peripheral artery disease (PAD) in the REACH Registry. *Defined as intermittent claudication with an ABI <0.90 and a history of intermittent claudication along with prior peripheral revascularization or amputation. HR indicates hazard ratio. Adapted from Kumbhani et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. ABI indicates ankle:brachial index.

**Figure 9.** Overview of recommendations for treatments that reduce the risk of major adverse cardiovascular events and limb vascular events and improve symptoms in patients with peripheral artery disease (PAD). ABI indicates ankle:brachial index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; MACE, major adverse cardiovascular events; and PAR, protease-activated receptor.
All patients with PAD should receive preventive interventions, including lifestyle modification and optimal management of atherosclerotic risk factors (Figure 9). The benefits of statin therapy may extend beyond reduction of MI, stroke, and cardiovascular death to improving functional status and reducing limb vascular events and amputation. Anti-platelet therapy also reduces the risks of MI, stroke, and cardiovascular death in patients with symptomatic PAD. Whether high-risk subgroups of patients with symptomatic PAD may benefit from dual antiplatelet therapy is suggested by findings from several studies, but additional trials specifically testing this possibility are needed for confirmation. Antithrombotic therapy with vitamin K antagonist therapy does not improve cardiovascular outcomes compared with aspirin and is associated with increased bleeding risk. Ongoing trials which are assessing the potential efficacy of newer antiplatelet agents and oral anticoagulants on cardiovascular risk in patients with PAD are in progress.

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