VDM Vascular Disease Management

REVIEW

Antiplatelets, Statins, and Cilostazol in Peripheral Artery Disease

Medical Therapy Is the Responsibility of the Interventionalist

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Abstract

Peripheral artery disease (PAD) is a common condition encountered in primary care and subspecialty clinics. Despite guidelines recommending antiplatelet agents, statins, and in some cases cilostazol, many patients with PAD are not receiving appropriate medications. Interventionalists who evaluate and treat these patients have a unique opportunity to prescribe appropriate cardioprotective medications, and to educate the primary care provider. In this article we will review guidelines for prescribing antiplatelet agents (aspirin and clopidogrel), statins, and cilostazol in patients with PAD; review evidence behind the guidelines; and present a "report card" of healthcare provider compliance with these guidelines. We will also describe some of the barriers that reduce clinician compliance with guidelines and present some strategies to overcome these barriers.

Peripheral artery disease (PAD) is commonly encountered in primary care and subspecialty clinics. Its prevalence — estimated to be 7.1 million in the United States[1] — increases with increasing age (>40 years) and with independently associated risk factors of diabetes, smoking, and hyperlipidemia. These risk factors have an additive effect on the development and severity of the disease.[2]

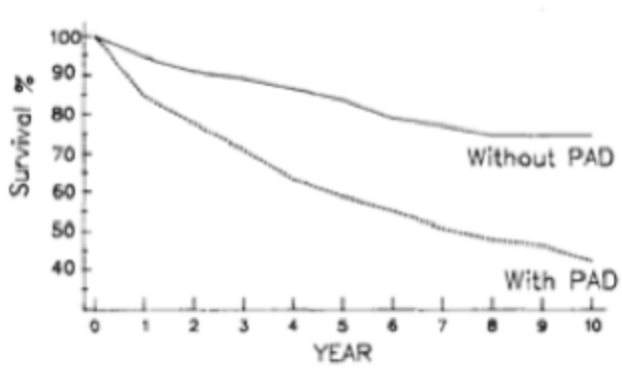

Figure 1. Patients with peripheral artery disease have lower survival rates than patients without peripheral artery disease. Reprinted with permission from Atherosclerosis.[4] Copyright 1991, Elsevier.

Approximately 50% of patients with PAD are asymptomatic and diagnosed by screening Ankle Brachial Index (ABI), 10% to 35% have claudication, and 1% to 2% have critical limb ischemia (CLI), defined as rest pain, tissue loss, or gangrene.[3] Patients with PAD (defined as ABI score <0.9) have lower survival (**Figure 1**)[4] and higher rates of cardiovascular and cerebrovascular events as compared to patients without PAD.[4,5-7] Symptom severity and lower ABI score have been correlated with greater functional decline and decreased survival (**Figure 2**).[4,5,8,9] The annual mortality among patients with critical limb ischemia, defined as an ABI <0.4, is approximately 25%, with most of the morbidity and mortality related to myocardial infarction (MI) and stroke.[10]

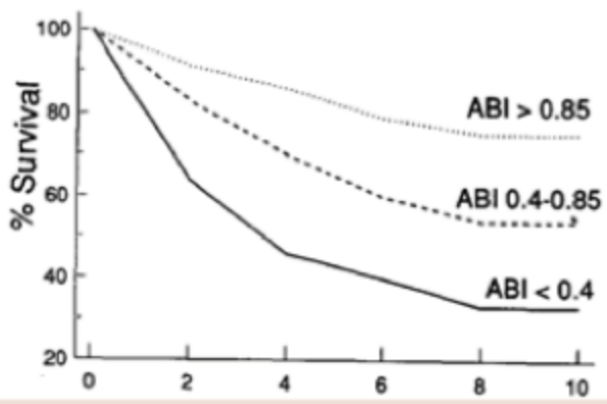

Figure 2. Survival curves stratified by ankle-brachial index. Low Ankle Brachial Index is associated with decreased survival. Reprinted with permission from Atherosclerosis.[4] Copyright 1991, Elsevier.

Even with known high prevalence and associated high cardiovascular morbidity and mortality, PAD remains under-recognized and undertreated. The PARTNERS (PAD Awareness, Risk and Treatment: New Resources for Survival) study, which evaluated approximately 7,000 patients aged 70 years or older, or aged 50 through 69 years with history of cigarette smoking or diabetes in primary care practices across the United States, showed that of patients with known PAD, only 83% were aware of their diagnosis, and only 49% of their physicians were aware of the diagnosis.[11]

The National Cholesterol Education Program (NCEP) expert panel considers PAD an equivalent to coronary artery disease (CAD), and therefore recommends that patients with PAD receive the same cardioprotective medication regimen as patients with CAD.[12] However, despite evidence from several studies showing that antiplatelet agents[13-15] and statins[16-18] reduce cardiovascular morbidity and mortality in patients with PAD, only 25% of the patients with PAD are receiving appropriate medical treatment.[19] This alarmingly low number may stem from poor provider awareness about how to manage PAD.[19] The recently published Performance Measures for Adults with PAD, which provide metrics for quality improvement and external reporting, recommend prescribing an antiplatelet and a statin.[20]

Interventionalists who treat patients with PAD have a unique opportunity to place patients on optimal cardioprotective therapy in accordance with the latest guidelines. The purpose of this article is to review guidelines for the use of antiplatelets (aspirin and clopidogrel), statins, and cilostazol; summarize evidence behind the guidelines; and present a "report card" of how we do as health care providers in adhering to these guidelines.

Antiplatelets

Aspirin: Guidelines

Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (class 1, level of evidence: B).[21]

Aspirin: Evidence Behind the Guidelines

In 2002, the Antithrombotic Trialists' Collaboration performed a meta-analysis examining the efficacy of antiplatelet agents on cardiovascular events (nonfatal MI, nonfatal stroke, and vascular death) in 135,000 patients (287 studies) with vascular disease (acute and previous MI, acute and previous stroke, or other high-risk conditions, such as lower extremity PAD).[15] The authors found that patients receiving antiplatelet therapy experienced a 22% odds reduction for adverse cardiovascular events compared with patients not receiving an antiplatelet agent ($P<.0001$). In a subset analysis of 42 trials including 9,214 patients with PAD, there was a 23% reduction in serious vascular events ($P<.004$) compared with controls.[15] Similar benefit was observed in patients with intermittent claudication as well as those undergoing peripheral bypass grafting and peripheral angioplasty.[15] The rate of cardiovascular events was similar in patients taking high doses vs low doses of aspirin. More recently, the CLIPS (Critical Leg Ischemia Prevention Study) trial[14] demonstrated reduction in cardiovascular events in patients randomized to aspirin versus placebo. This study involved patients with symptomatic (claudicant) or asymptomatic PAD (ABI <0.85) documented by angiography or ultrasound. The trial was stopped early because of poor patient recruitment.

Recent papers raised doubts regarding the benefits of aspirin in patients with PAD. A meta-analysis including 18 trials compared the effects of aspirin (with or without dipyridamole) vs controls in patients with PAD.[22] Out of 5,269 patients in this trial, 2,823 of whom were taking aspirin (with or without dipyridamole) there was no statistically significant reduction in the primary end point of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death) (pooled relative risk [RR] 0.88; $P=.13$). However, associations of aspirin therapy with the individual components of the primary end points showed that the risk of nonfatal stroke was significantly lower in the aspirin group than in the placebo group (RR 0.66; $P=.02$). One caveat about this trial is that it may have missed smaller but beneficial effects of aspirin as it was designed to detect a 25% or greater reduction in cardiovascular events.

The POPADAD (Prevention of Progression of Asymptomatic Diabetic Arterial Disease) trial[23] evaluated the effects of aspirin versus placebo in 1,276 patients with diabetes and asymptomatic PAD (ABI <0.99). Aspirin therapy failed to show any benefits in reducing cardiovascular events and mortality. The AAA trial (Aspirin for Asymptomatic Atherosclerosis)[24] randomized 3,350 asymptomatic patients with ABI <0.95 to receive either aspirin or placebo for mean duration of 8.2 years. Aspirin therapy failed to show any benefits in reduction of primary endpoint, a composite of initial fatal or nonfatal coronary event, stroke, or revascularization. One limitation of the study was that 40% of the patients were noncompliant with the medication regimen.

Because recent trials showed a neutral effect of aspirin, the level of evidence for prescribing aspirin in patients with PAD has been changed from A to B in the 2011 ACCF/AHA focused update guidelines.[21]

Clopidogrel: Guidelines

Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (class 1, level of evidence: B).[21]

Evidence Behind the Guidelines

Clopidogrel is a thienopyridine derivative that decreases platelet activation. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial[13] randomized 19,185 high-risk patients (recent MI, recent stroke, or PAD) to receive either clopidogrel or aspirin for a mean duration of 1.91 years. The primary endpoint was a composite of ischemic stroke, MI, or vascular death. Patients randomized to clopidogrel experienced an 8.7% relative risk reduction in vascular events ($P=.043$). In the subgroup of patients with PAD, patients randomized to clopidogrel had 23.8% relative risk reduction in vascular events ($P=.0028$) (**Figure 3**).

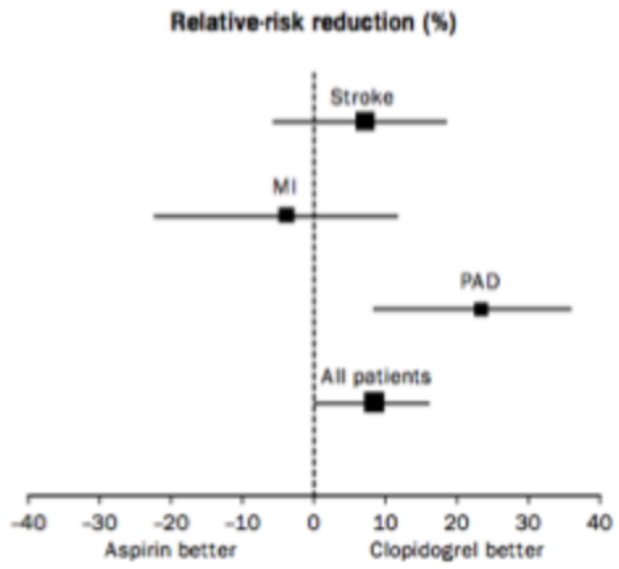

Figure 3. There was a 23.8% relative risk reduction with clopidogrel in vascular events in patients with PAD. Reprinted with permission from The Lancet.[13] Copyright 1996, Elsevier.

Combination Antiplatelet Therapy

Guidelines

The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk (class IIb, level of evidence: B).[21]

Evidence Behind the Guidelines

The CHARISMA trial directly compared dual antiplatelet therapy (aspirin and clopidogrel) to aspirin alone in 15,603 patients who were at high risk for cardiovascular events.[25] After a median of 28 months follow-up, no difference was seen in the primary endpoint, a composite of myocardial infarction, stroke, or death from cardiovascular causes between two treatment groups. In subgroup of patients with PAD, combination therapy failed to show any benefits. Two post-hoc analyses[26,27] of the CHARSIMA trial identified potential benefits to combination antiplatelet therapy over aspirin alone. However, this observation needs to be validated with a well-designed, randomized control trial. Keeping these results in mind the 2011 focused updated ACCF/AHA guidelines included new recommendation for dual antiplatelet therapy.[21]

Statins

Guidelines

Treatment with a statin is indicated for all patients with PAD to achieve a target low density lipoprotein (LDL) cholesterol level of less than 100 mg/dL (class 1, level of evidence: B).[3]

Treatment with a statin medication to achieve a target LDL cholesterol level of less than 70 mg/dL is reasonable for patients with lower extremity PAD at very high risk of ischemic events (class IIa, level of evidence: B).[3]

Evidence Behind the Guidelines

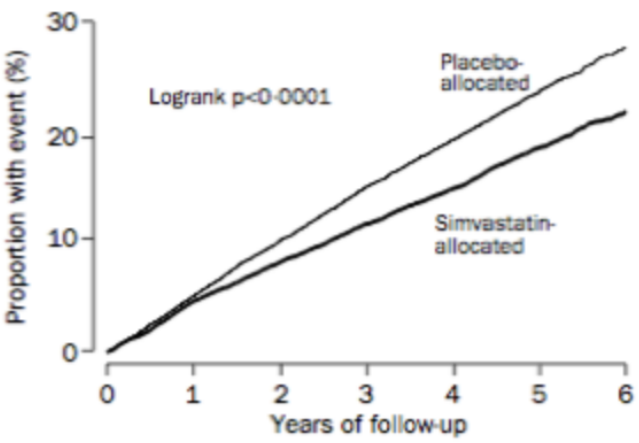

Figure 4. Life-table plot of effects of simvastatin allocation on percentage of patients having major vascular events. Reprinted with permission from The Lancet.[16] Copyright 2002, Elsevier.

The Heart Protection Study randomized 20,536 high risk patients with CAD, cerebrovascular, PAD, or diabetes to receive 40 mg of simvastatin daily or placebo.[16] After 5 years of follow-up, patients allocated to the simvastatin group enjoyed a 24% relative risk reduction in the occurrence of MI, stroke, and coronary and noncoronary revascularization (*P*=.0001, **Figure 4**). Patients receiving simvastatin also had 17% proportional reduction in mortality due to vascular causes. A subgroup analysis found 22% reduction in the rate of first vascular events in 6,748 patients with PAD regardless of their presenting cholesterol levels.[28]

Statin use is associated with decreased mortality in CLI patients undergoing infrainguinal bypass graft surgery[17] or endovascular repair.[18] In the latter series, patients with CLI who underwent endovascular revascularization were categorized according to whether they were taking a statin at the time of revascularization. At 24 months after revascularization, patients who were prescribed a statin had significantly better primary patency, secondary patency, limb salvage, and overall survival than patients who were not taking a statin. Moreover, the beneficial effects of statins were independent of the total cholesterol and LDL levels.[18]

Cilostazol

Guidelines

Cilostazol (100 mg orally 2 times per day) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure) (class 1, level of evidence: A).[3]

A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure) (class 1, level of evidence: A).[3]

Evidence Behind the Guidelines

Cilostazol is a phosphodiesterase type 3 inhibitor that has antiplatelet and vasodilatory properties.[29] Several trials have shown that cilostazol increases walking distance compared with placebo in patients with intermittent claudication.[30-33] A cilostazol dose of 100 mg twice daily is more effective than 50 mg twice daily.[33]

Cilostazol also has been shown to reduce restenosis,[34-37] decrease the rate of target vessel revascularization (TVR),[34] and improve limb salvage[35] in patients who have undergone infrainguinal intervention. In one trial, 80 patients with intermittent claudication due to

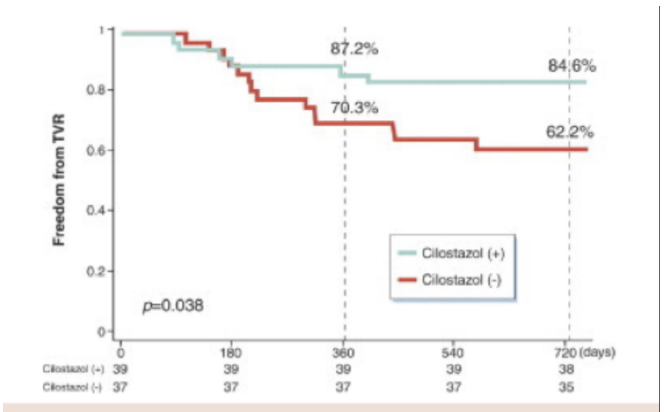

Figure 5. Freedom from target vessel revascularization after 24 months was significantly higher in the cilostazol (+) group (green line) compared with the cilostazol (-) control group (red line) (84.6% vs 62.2%, P=.038). Reprinted with permission from the Journal of American College of Cardiology.[34] Copyright 2009, Elsevier.

femoropopliteal lesion (without an inflow lesion, with an outflow artery, and with symptoms that were not improved with pharmacological therapy or exercise) were randomized to cilostazol or placebo. Patients underwent either balloon angioplasty or stent placement (stent was placed if after 60 sec of balloon angioplasty the residual stenosis was >30%). The lesion length was 121 ± 67.3 mm and 131.5 ± 84.0 mm in patients who did and did not receive cilostazol, respectively. There was significant reduction in the primary end point of TVR at 2 years follow-up in the patients receiving cilostazol (84.6% vs 62.2%; *P*=.04, **Figure 5**). Patients receiving cilostazol also had better secondary outcomes, which included lower binary restenosis rate (43.6% vs 70.3%; *P*=.02), freedom from target lesion revascularization (87.2% vs 67.6%; *P*<.05) and freedom from major adverse cardiovascular events (MACE) defined as death, nonfatal MI, stroke, percutaneous or surgical revascularization, and leg amputation (79.5% vs 48.7%; *P*=.006).[34]

In another series, 618 patients (356 with and 262 without cilostazol) with CLI who underwent endovascular therapy were retrospectively analyzed. Patients who were receiving cilostazol had better amputation-free survival (47.7% vs 32.7%; log rank *P*<.001), limb salvage (86.6% vs 75.3%; log rank *P*=.004), and freedom from surgical conversion (91.0% vs 81.2%; log rank *P*=.001) than patients who were not taking cilostazol. However, no significant difference was observed between two groups in terms of overall survival and freedom from repeat revascularization.[35]

Pentoxifylline

Pentoxifylline is used by some providers as a treatment for claudication. The data to support its use in patients with claudication are insufficient. Two meta-analyses of randomized, placebo controlled trials found only marginal benefit of pentoxifylline.[38,39] ACC/AHA 2005 practice guidelines for management of patients with PAD concluded that clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established and gave class IIB (level of evidence: C) recommendation for its use.[3]

Report Card of Physician Compliance and Conclusion

Table 1. Percentage of patients with peripheral artery disease receiving antiplatelet agents and statins in major trials/case series (arranged chronologically).

Name/author of study	Characteristics of study participants	Year of publication	N (number of patients in the study)	Patients receiving antiplatelet agents (%)	Patients receiving statins (%)
Mondillo et al.[42]	Claudicants	2003	86	61	NA
McDermott et al.[43]	Ankle Brachial Index <0.9	2003	392	Not reported	45
PREVENT III[44]	Critical limb ischemia	2005	1,404	67	46
BASIL (bypass versus angioplasty in severe ischemia of the leg)[45]	Critical limb ischemia	2005	452	58	34
CARP (coronary artery revascularization prophylaxis)[46]	Critical limb ischemia	2006	307	80	46
Giri et al.[47]	Ankle Brachial Index <0.9	2006	332	Not reported	46
CASTLE study[48]	Claudicants	2008	1,435	72	71
Soga et al.[35]	Critical limb ischemia	2011	618	85	22
Aiello et al.[18]	Critical limb ischemia	2012	646	78	49

Table 1 shows a "report card" in terms of prescribing antiplatelet agents and statins in several major trials and case series. The trend for prescribing antiplatelet agents seems to be increasing in the recent trials but still remains around 80%. Except for the CASTLE trial, the use of statins in most trials remains disappointing, with utilization rates below 50%. Thus, even in highly controlled research settings, it appears that patients with PAD remain undertreated with cardioprotective medications.

Table 2. Recognized barriers to compliance with the guidelines and suggested interventions that could improve physician compliance.

Recognized Barriers
Poor provider awareness
Physician disagreement with the guidelines
Guidelines that are difficult/not convenient to use
Physician lack of confidence and/or experience to follow the recommended guidelines
Lack of motivation and provider practice habits
Deficiency of resources (computer reminder system, difficulty accessing guidelines)
Limited reimbursement
Patient related limiting factors (unawareness, patient's personal preference)
Suggested Interventions
Provider education (seminars, expert lectures etc.)
Close communication between referring and front line providers
Easily accessible information (handouts, information cards etc.)
Strategies to measure performance of providers adhering to guidelines
Feedback to individual providers
Pay per performance (incentive for providers who have high adherence rate)
Good IT support (easy access to guidelines, computer reminders etc.)
Patient education (seminars, giving handouts at the end of visit)

Studies have suggested a variety of physician-related factors that could be responsible for nonadherence with the guidelines. These factors include lack of physician awareness or disagreement with the guidelines, lack of confidence that they could adhere to the guideline recommendations, and their belief that following guidelines will not change patient outcomes. Lack of motivation and physician habits are also postulated as a barrier to adhering to guidelines.[40] Other external factors such as lack of time, lack of resources (e.g., computer reminder system), limited reimbursement and presence of contradictory guidelines also have been shown to decrease physician compliance.[40,41] **Table 2** summarizes potential barriers to compliance with the guidelines and suggests possible interventions. **Table 3** provides a summary of the recommended medical treatment in patients with PAD.

Table 3. Recommended medical treatment in patients with peripheral artery disease.

Treatment with aspirin is indicated in all patients with peripheral artery disease to reduce the risk of myocardial infarction), stroke, or vascular death
Clopidogrel is a safe and effective alternative to aspirin in patients with peripheral artery disease
Combination antiplatelet therapy could be considered in some patients who are at high risk for cardiovascular events and low risk of bleeding
Treatment with statins is recommended for all patients with peripheral artery disease for low-density lipoprotein goal of <100 mg per dL and <70 mg per dL in high risk patients
Cilostazol is shown to provide symptomatic benefit and is recommended for all patients with symptomatic peripheral artery disease (in absence of congestive heart failure)

Steps must be taken to improve physician awareness and compliance with PAD guidelines. First and foremost, primary care physicians need to be aware of the signs and symptoms of PAD, as well as recommendations for managing these patients. Specialists who see these patients in consultation whether in vascular medicine, interventional cardiology with special training in endovascular medicine, or vascular surgery should insure that each patient is on optimal cardioprotective therapy. Vascular specialists are uniquely positioned to educate referring providers on the latest recommendations for managing PAD.

The prevalence of PAD is going to increase with the aging of the United States population. Increased physician awareness of how to manage PAD not only will improve compliance with the guidelines, but also may help providers improve the lives of their patients.

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