A Review of the Role of Anticoagulation in the Treatment of Peripheral Arterial Disease

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Abstract

Peripheral arterial disease (PAD) is a major medical/surgical problem associated with high risk for coronary heart disease (CHD). Anticoagulation plays a significant role in the management of the PAD patient. However, evidence-based medicine supports only select anticoagulants, mainly antiplatelet agents. The available anticoagulant classes, their individual medications, and the mechanisms of action are described. Dextran 40, platelet glycoprotein (GP) IIb/IIIa receptor antagonists, direct thrombin (factor IIa, FIIa) inhibitors, and factor Xa (FXa) inhibitors do not, at this juncture, appear to have a significant role to play in the PAD patient. Aspirin has been used in PAD patients for a few decades, as has warfarin, but the role of warfarin is very limited. An attempt has been made to place each medication and its function in context all the way to the present with oral direct thrombin (FIIa) and FXa inhibitors described. These inhibitors may ultimately play an, as yet, undefined role in PAD. Specific use of anticoagulants in PAD patients is described and aspirin still stands out as a fundamental therapy. The thienopyridines, especially clopidogrel, have their established place and there is some evidence for benefit from the use of clopidogrel in dual therapy with aspirin. Dipyridamole, especially with aspirin as dual therapy, and cilostazol also have their evidence-based niches. The main role played by warfarin is for the patient with a vein graft in the arterial circulation. Heparin retains significant procedural importance. For now, Class I, Level of Evidence A center around aspirin for the PAD patient with clopidogrel, an alternative agent.

Keywords

- anticoagulation
- aspirin
- cardiovascular disease
- coronary artery
- peripheral arterial disease
- risk factors
- thienopyridines

Peripheral arterial disease (PAD) is a major cardiovascular (CV) problem in the United States and the rest of the world. For the United States, from 1985 to 1987, the National Center for Health reported that an estimated total of 413,000 patients (229,000 men and 184,000 women) were discharged from a hospital with an associated diagnosis of PAD.[1] The prevalence of PAD in primary care practices is high but physician awareness appears low. Data confirming this was obtained in a study of 350 primary care practices throughout the United States.[2] In this study, it was found that in patients with known prior PAD, only 49% of their physicians knew of this diagnosis in their specific individual patient. When PAD is present, there is a very significant likelihood of having coronary heart disease (CHD). This was shown in an evaluation by Sukhija et al, who studied the ankle-brachial index (ABI), and correlated it with the severity of CHD in 273 patients, mean age 71 years.[3] These authors used the ABI to correlate the presence of PAD with angiographically present CHD of $>$ 50% occlusion. Of 155 patients with an ABI $<$ 0.40, 130 (84%) had 3- or 4-vessel CHD, 17 (11%) had 2-vessel CHD and 8 (5%) had 1-vessel CHD. Of 80 patients with an ABI of 0.40 to 0.69, 37 (46%) had 3- or 4-vessel CHD, 33 (41%) had 2-vessel CHD and 10 (13%) had 1-vessel CHD. Therefore, with this severe PAD group with ABI $<$ 0.40, the incidence of CHD was almost 100%, and the association of CHD was still quite significant with less severe PAD. The lower the ABI, the higher the prevalence of 3- or 4-vessel CHD. It is essential for clinicians, whether in primary or CV specialties, to make and confirm the diagnosis of PAD so that optimal medical management is offered to the patient. This is important for the proper use of

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anticoagulation as discussed in this article, as well as prescribing other essential preventive measures such as the use of statins to markedly decrease low-density lipoproteins (LDL). There is actually more data to support the use of various forms of anticoagulation in CHD patients. In this context, the purpose of this article is to describe the available anticoagulant medications and clarify their role in the medical management of PAD.

Description of Commonly Used Anticoagulant Medications

Aspirin is a cyclooxygenase (COX) inhibitor that results in permanent inactivation of COX activity of prostaglandin H (PGH)-synthase-1 and -2, known as COX-1 and COX-2. These isozymes catalyze the first step in the conversion of arachidonic acid to PGH2, which is the immediate precursor of multiple prostaglandins, including thromboxane A2. The inhibition of COX-1-dependent platelet function occurs with low doses of aspirin, whereas COX-2-dependent processes, which include hyperalgesia and inflammation, require much larger doses of aspirin.[4–7]

$P2Y_{12}$ inhibitors is a class of medication that involves the thienopyridines which cause irreversible alterations of the platelet receptor $P2Y_{12}$. This receptor mediates inhibition of adenosine diphosphate (ADP) stimulated adenyl cyclase activity.[6] The thienopyridines include clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta). Clopidogrel itself is an oral pro-drug and it is its subsequent active metabolite that couples via a disulfide bridge to the $P2Y_{12}$ receptor. There is then a cumulative inhibition of ADP-induced platelet aggregation followed by slow recovery of platelet function after drug withdrawal.[8] Prasugrel is also a thienopyridine oral pro-drug that is converted into an irreversible $P2Y_{12}$ receptor inhibitor.[9] Prasugrel inhibits platelet aggregation with greater rapidity, greater consistency, and to a greater extent than do standard and higher doses of clopidogrel as studied in both healthy volunteers and in CHD patients. On the other hand, ticagrelor binds the $P2Y_{12}$ receptor reversibly and noncompetitively blocks ADP-induced platelet activation.[10] Metabolic activation is not required with ticagrelor and it demonstrates greater platelet inhibition with a faster offset of action in comparison to clopidogrel. This can be a distinct advantage when bleeding is problematic.

GPIIb/IIIa receptor antagonists react with platelet glycoprotein (GP) IIb/IIIa complex (αIIbβ3 integrin).[11] This can markedly prolong the bleeding time. There are three approved GPIIb/IIIa receptor antagonists in the United States: abciximab (ReoPro), tirofiban (Aggrastat), and eptifibatide (Integrilin).

Dipyridamole (Aggrenox) is a pyrimidopyrimidine derivative that first appeared in the early 1960s as a coronary vasodilator.[12] It was subsequently shown to inhibit the adhesion of platelets to glass ex vivo in patients with CHD and also to decrease thrombus formation in experimental models. Clinical efficacy was initially questioned, but subsequently, the medication was reformulated to improve its relatively low bioavailability. Subsequently, the combination of dipyridamole with aspirin resulted in increased effectiveness as compared with each medication used alone.[13] Bleeding complications have been found not to be increased with dipyridamole. Other possible beneficial effects of dipyridamole include inhibition of inflammation and matrix metalloproteinase expression, both of which are involved in atherosclerosis.[14]

Cilostazol (Pletal) is a phosphodiesterase 3 (PDE3) inhibitor with antiplatelet, antithrombotic, and vasodilatory effects.[15] It was initially developed as a selective PDE3 inhibitor and this inhibition in platelets and vascular smooth muscle cells was expected to provide an antiplatelet effect, vasodilatation, and an antithrombotic effect.[16]

Warfarin (Coumadin) has been a widely used anticoagulant. The fascinating story of warfarin began on the great plains of Canada and northern United States in the 1920s, when it was found that previously healthy cattle were dying of internal bleeding of unknown etiology.[17] It was found that the cattle had grazed on sweet clover hay and that the greatest incidence of bleeding occurred when the climate, and therefore the hay, were damp. Normally, such moldy hay would have been discarded but not during the financial hardship period of the 1920s. Fractionation of compounds found in the hay ultimately yielded warfarin (Coumadin), a vitamin K antagonist, as a possible rodenticide in the 1940s. Warfarin is still in widespread use, with clinical control significantly improved by changing the assay from prothrombin time to International Normalized Ratio.

Direct thrombin (factor IIa, FIIa) inhibitors in oral form are exemplified by dabigatran (Pradaxa). The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Trial with dabigatran etexilate, studied this new oral direct thrombin inhibitor in patients with atrial fibrillation.[18] Dabigatran has the major advantage that clinical laboratory monitoring is not necessary but the disadvantage in that there is no medication for reversal of its anticoagulation. Nevertheless, this new medication appears to be a major contribution to anticoagulation and to the management of the patient with atrial fibrillation and it has been approved for this indication.

Bivalirudin (Angiomax) is a 20-amino acid synthetic peptide that is a direct thrombin (FIIa) inhibitor.[19] It is administered by intravenous injection and results in almost immediate anticoagulant activity. In contrast to unfractionated heparin (UFH), bivalirudin has a short elimination half-life of 25 minutes when renal function is normal.

Factor Xa inhibitors include rivaroxaban (Xarelto) and apixaban (Eliquis) as direct inhibitors. The Rivaroxaban Once daily oral direct Factor Xa (FXa) inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial showed that rivaroxaban is noninferior to warfarin for stroke prevention or systemic embolism in patients with atrial fibrillation.[20] On the other hand, apixaban was shown in the Apixaban for Reduction in Stroke and other ThromboembboLic events in atrial fibrillation (ARISTOTLE) trial, to be superior to warfarin in preventing stroke or systemic embolism in atrial fibrillation, had fewer bleeding complication,

and had a lower mortality compared with warfarin.[21] Both of these direct FXa inhibitors do not require clinical laboratory monitoring, but, as in the case of dabigatran, have no reversal by another medication.

Heparin is a glycosaminoglycan composed of chains of alternating residues of D-glucosamine and uronic acid. Its major anticoagulant effect occurs via a unique pentasaccharide with a high-affinity binding sequence to antithrombin III (ATIII).[22] In this sequence, conformational change in ATIII occurs, thereby markedly accelerating its ability to inactivate thrombin (FIIa), FXa, and FIXa; of these three enzymes, thrombin is the most sensitive to heparin inhibition.

Dextran 40 has antithrombotic and antiplatelet effects and these are poorly understood in PAD. Robless et al studied the effects of dextran 40 on platelet function in control subjects and PAD patients using whole blood methods.[23] They found that dextran 40 reduces spontaneous and agonist-induced platelet aggregation as well as the surface expression of markers of platelet activation in PAD patients.

Specific Use of Anticoagulants in PAD Patients

Aspirin used in PAD patients undergoing peripheral arterial interventions and receiving antithrombotic agents, appears to be just as effective, or more so, when started before the intervention, compared with clopidogrel or abciximab.[24] Aspirin alone, or in combination with other antiplatelet drugs, has proven effective in reducing graft thrombosis. Establishment of aspirin as an agent that could alter platelet function appears to have occurred in 1968 when it was observed that aspirin ingestion resulted in altered platelet aggregation by connective tissue and was associated with decreased release of platelet ADP.[25] In the Physicians' Health Study group, continuous administration of low-dose aspirin to healthy men reduced the need for peripheral arterial surgery.[26] The Dutch Bypass Oral Anticoagulants study showed that aspirin was better for the prevention of prosthetic graft occlusion when compared with oral anticoagulation with phenprocoumon or acenocoumarol. Phenprocoumon and acenocoumarol were more effective in preventing infrainguinal-vein-graft occlusion).[27] Aspirin, as a single antiplatelet therapy, has excellent support from clinical evidence, used for primary and secondary prevention of CV events in most patients with both asymptomatic and symptomatic PAD.[28] Many clinicians consider that additional medications for relief of lower extremity symptoms should only be considered after exercise programs, cessation of smoking, and evaluation for peripheral artery revascularization (►**Table 1**).

$P2Y_{12}$ inhibitors (thienopyridines) are used extensively in PAD. Thienopyridines have good clinical evidence for clinical benefit in CHD. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel in acute coronary syndrome (ACS) patients having a percutaneous coronary intervention resulted in

Table 1 Medications used in anticoagulation

Specific medications	Specific role in peripheral arterial disease
Bivalirudin	Possible decrease in adverse events compared with heparin
Cilostazol	Relieve ischemia of chronic arterial occlusion
Dipyridamole	Prevention of ischemic stroke and transient ischemic attack. Usually used with aspirin
Dual antiplatelet therapy	
Aspirin and dipyridamole	To possibly decrease progression of peripheral arterial disease
Aspirin and clopidogrel	When risk of reocclusion increased
	Possible value before/after stenting
	Possible value with prosthetic grafts
Heparin	Prevention of thrombosis with increased graft patency out to 30 days
Platelet inhibitors	
Aspirin	Can still be considered gold standard in PAD
Thienopyridines ($P2Y_{12}$ inhibitors)	Primary/secondary prevention of cardiovascular events
Clopidogrel, prasugrel, ticagrelor	Prevention of prosthetic graft occlusion Alternative when aspirin not tolerated
Warfarin	Specific advantage in venous grafts
Direct thrombin (factor IIa) inhibitors	No established role
Factor Xa inhibitors	No established role
Dextran 40	No established role
GPIIb/IIIa receptor antagonists	No established role

Abbreviations: GPIIb/IIIa, platelet glycoprotein IIb/IIIa; PAD, peripheral arterial disease.

significantly decreased rates of ischemic events, including stent thrombosis, compared with patients using clopidogrel.[29] However, there was an increased risk of major bleeding with prasugrel, including fatal hemorrhage, although overall mortality did not differ significantly between prasugrel and clopidogrel use. Ticagrelor is an oral, direct-acting and reversible $P2Y_{12}$ inhibitor.[30] Its peak concentration in the blood occurs 2 to 3 hours after ingestion.[6] In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was compared with clopidogrel in patients with ACS who were awaiting coronary artery bypass graft (CABG) surgery.[31] A subgroup of patients undergoing CABG surgery within seven days of taking ticagrelor versus clopidogrel was assessed. It was found that ticagrelor compared with clopidogrel was associated with a significant decrease in total and CV mortality, with no increased risk of bleeding related to CABG surgery. Significant clinical benefits have been demonstrated for the use of either prasugrel or ticagrelor, instead of clopidogrel.[6] Consideration for their use in all patients with ACS who do not have a high-bleeding risk appears appropriate in association with aspirin. Prasugrel appears more effective than clopidogrel in preventing stent thrombosis and appears appropriate, if there is not an increased bleeding risk.[32] Specific prasugrel indications could be envisioned for prior stent thrombosis, unprotected left main stenting or complex CHD, even for several years. Ticagrelor, on the other hand, may have an advantage when started well before percutaneous coronary intervention among patients with moderately increased bleeding risk. An additional ticagrelor advantage may be associated with its use in the patient likely to need semi-urgent CABG surgery. In addition to the much more rapid initial platelet inhibition with ticagrelor compared with clopidogrel, there is a much faster offset of platelet inhibition after ticagrelor discontinuation. This can be calculated as a 4- to 72-hour offset slope for platelet inhibition with offset of platelet inhibition 1.04% per hour for ticagrelor versus 0.48% per hour for clopidogrel. The shorter time for reversibility with ticagrelor could be a significant advantage as compared with clopidogrel.[33] Clopidogrel appears to have another disadvantage in that, in some patients, it has a less dependable responsiveness and lower bioavailability in association with its pro-drug mode and conversion step to the active form, as well as an increased susceptibility to adverse clopidogrel–drug interactions.[34,35]

In PAD, the thienopyridine clopidogrel has been studied as an alternative antiplatelet agent to reduce platelet aggregation after endovascular procedures. One double-blind, randomized, placebo-controlled trial evaluated the antiplatelet effects of clopidogrel and aspirin versus placebo and aspirin after lower limb angioplasty.[36] The investigators also evaluated whether markers of coagulation activation, D-dimer and thrombin–antithrombin complexes (TAT), were affected by clopidogrel in patients undergoing peripheral angioplasty. Peripheral intervention resulted in significant increases in TAT and D-dimer levels, but the addition of clopidogrel to the therapy with aspirin had no effect on the levels of these markers before or after endovascular intervention.[37] Clopidogrel might represent a useful alternative in cases in which aspirin is not tolerated, or as a combination therapy with aspirin when increased risk factors for re-occlusion are detected, although supportive data are minimal. The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) study was started to evaluate the efficacy and safety of this dual therapy after femoropopliteal revascularization. However, the study was stopped because of insufficient recruitment.[38] Many interventionalists have begun to use combined platelet inhibition with aspirin and clopidogrel before and after angioplasty and stenting in peripheral arteries. Although this strategy has not been studied prospectively in randomized trials, it appears to be a reasonable approach to reduce acute and subacute thrombotic complications after endovascular procedures.[39]

GPIIb/IIIa receptor antagonists have not been shown to play a significant role in PAD patients. Most clinical evidence is with CHD patients in very special situations. The benefit to risk ratio of the three GPIIb/IIIa receptor antagonists is quite uncertain for patients with ACS who are not undergoing early revascularization. On the other hand, for the high-risk ACS patient undergoing PCI, the addition of a GPIIb/IIIa receptor antagonist has been shown to reduce the risk of thrombotic complications related to the procedure.[6]

Dipyridamole has been used successfully in PAD patients. In the European Stroke Prevention Study-2 (ESPS-2), aspirin 25 mg twice a day and modified-release dipyridamole 200 mg twice a day, were both equally effective in the secondary prevention of ischemic stroke and transient ischemic attack.[13] However, dipyridamole has generally been used in association with dual antiplatelet therapy.

Cilostazol in PAD has clinical indications for the treatment of intermittent claudication in the United States and in Japan for the treatment of ischemic signs and symptoms associated with chronic arterial occlusion. The major established benefit of cilostazol in PAD patients is an increase in walking distance and delay in the time point for significant claudication.[40] In the Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) study, it was found that, compared with aspirin, cilostazol significantly inhibited the progression of carotid intima-media thickness in type 2 diabetic patients suspected of PAD.[15] In the second Cilostazol for Prevention of Secondary Stroke (CSPS 2) trial, cilostazol was reported to be noninferior, and possibly superior, to aspirin for the prevention of stroke in patients with a previous cerebral infarct.[41] In addition, cilostazol was associated with fewer hemorrhagic events than aspirin. The possible use of cilostazol for the prevention of noncardioembolic stroke has been considered. There is confusion that PAD only involves the lower extremities but the National Heart, Lung and Blood Institute defines PAD as usually affecting the arteries in the legs but adds that the definition extend to arteries involving the head, arms, kidneys, and abdominal area.[42] Therefore, stroke can be considered with PAD, although this is not universally accepted.

Warfarin has a role in the treatment of PAD patients. However, anticoagulation with warfarin is not routinely used after a bypass procedure. In Sweden, Arfvidsson et al studied the influence of warfarin treatment on patency and limb salvage after peripheral arterial bypass procedures.[43]

Their results demonstrated that warfarin therapy does not improve outcome in routine infrainguinal bypass procedures. However, Sarac et al showed that warfarin improves the patency rate of vein graft and limb salvage for patients at high risk for graft failure.[44] The Dutch Bypass Oral Anticoagulants or Aspirin study compared oral anticoagulants versus aspirin for improved infrainguinal graft patency with subgroup analysis of prosthetic grafts.[27] Subgroup analysis demonstrated the beneficial effects of aspirin over therapeutic dose anticoagulants such that 15 patients needed to be treated to prevent one occlusion. The risk of significant bleeding was only 2.5% per year with aspirin versus 4.7% with a warfarin congener.[27] Overall, there are no evidence-based randomized studies currently available to support the use of anticoagulation to improve prosthetic graft patency. For <6 mm diameter prosthetic grafts, or to prevent worsened limb ischemia when occlusion occurs, trends in some studies would suggest some benefit of long-term anticoagulation after prosthetic infrainguinal bypass grafting.[45] A recent Cochrane review of trials suggested that patients undergoing venous grafts were more likely to benefit from treatment with vitamin K antagonists such as warfarin, than platelet inhibitors while patients receiving a prosthetic graft may benefit from platelet inhibitors such as aspirin.[46]

Direct thrombin (FIIa) inhibitors and FXa inhibitors have not played a significant role in PAD patients and there is no clinical approval for this use (►**Table 1**).

Bivalirudin has been shown to be advantageous in unstable angina patients undergoing PCI.[19] Experience with bivalirudin is less in PAD patients. Nevertheless, data appear favorable with bivalirudin in PAD with low rates of major bleeding complications and decreased adverse events compared with previous data with UFH. Another advantage of bivalirudin over UFH occurs in patients with heparin-induced thrombocytopenia. Significant thrombocytopenia is not associated with bivalirudin. Therefore, observational studies point to the safety and effectiveness of bivalirudin in PAD and suggest some additional benefit such as early sheath removal, earlier ambulation, and possibly lower major complication rates.

Heparin plays an important role in PAD patients. Unfractionated heparin (UFH) is usually used during bypass procedures. It is typically given 3 to 5 minute before cross-clamping of the artery. A commonly used dose is 100 to 150 units/kg given intravenously. This is monitored with activated clotting time (ACT) in the operating room. An additional dose is given on the basis of ACT value. The half-life of UFH is $\sim$ 80 to 90 minutes. This approach has been shown to prevent stasis thrombosis. In addition, Thompson et al have reported intraoperative UFH provides prophylaxis against perioperative myocardial infarction (MI) in abdominal aortic aneurysm surgery.[47] Low molecular weight heparins (LMWH) are not widely used because of their long duration of action that cannot be completely reversed with protamine.[48,49] Norgren and his group reported from a randomized trial that LMWH was as effective as UFH in preventing thrombosis, without excess bleeding or hemorrhagic complications during peripheral vascular reconstruction (carotid surgery not included) in terms of 1-day and 30-day graft patency, operative blood loss, and hemorrhagic complications. LMWH or UFH were given intravenously immediately before clamping.[50]

Dual antiplatelet therapy plays a significant role in PAD. In their study, Hess et al found aspirin and dipyridamole delays the progression of PAD.[51] This was a prospective double-blind arteriographically controlled trial. The Antiplatelet Trialists' Collaboration also reported that antiplatelet therapy reduced the risks of vascular occlusion in a wide range of patients at risk for this complication.[52] Bhatt et al. reported that clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death.[53] The Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease (CASPAR) trial showed that combination of clopidogrel plus aspirin did not provide overall improvement for patients requiring below knee bypass grafts.[54] However, subgroup analysis suggests benefit of dual antiplatelet therapy in patients who were bypassed with prosthetic grafts. In their randomized placebo-controlled study involving 20 patients undergoing infrainguinal bypass surgery, Smout et al showed that the addition of clopidogrel to aspirin reduced platelet activation measured by platelet aggregation and flow cytometry.[55] Such a study supports the performance of a long-term trial with clinical endpoints.

Dextran 40 has been used in PAD patients. The efficacy of dextran 40 in preventing early postoperative thrombosis following difficult bypass procedures was studied by Rutherford et al.[56] This study failed to show any discernible effect. Since then, Katz and Kohl reported their experience with dextran 40.[57] This study was designed to determine the effect of dextran 40 on the early patency of autogenous infrainguinal bypass grafts. They concluded that the use of dextran 40 cannot be recommended for routine use in PAD.

Conclusions

It appears appropriate to begin this conclusion section with a summary of the 2011 focused update of the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines Class I, Level of Evidence A.[58] In these ACCF/AHA highest class and level guidelines, antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in patients with symptomatic lower extremity PAD. Aspirin is generally recommended when clopidogrel (a thienopyridine), is given, even though clopidogrel is an effective alternative antiplatelet agent itself. Oral anticoagulation with warfarin is considered Class III and of no benefit to reduce adverse CV ischemic events in patients with lower extremity PAD. It therefore appears established that antiplatelet agents, particularly aspirin, have a beneficial effect in reducing all cause mortality and fatal CV events in patients with PAD, and they improve patency and outcomes after peripheral vascular percutaneous or surgical interventions. Current evidence for clopidogrel and the newer thienopyridine antiplatelet agents, while promising, needs additional studies to compare the effects of each agent against aspirin and assess benefits versus risk of dual antiplatelet therapy in PAD. Regarding the newer

thienopyridines (prasugrel and ticagrelor), they have specific evidence-based uses in CHD. There is then the temptation to extrapolate their use to PAD. However, until specific evidence with PAD is available, such use should be limited to situations of clopidogrel ineffectiveness or intolerance. More recent antithrombotic agents, such as dabigatran, rivaroxaban, and apixaban, will also need assessment in patients with PAD.

References

1 Gillum RF. Peripheral arterial occlusive disease of the extremities in the United States: hospitalization and mortality. Am Heart J 1990;120(6 Pt 1):1414–1418
2 Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286(11):1317–1324
3 Sukhija R, Aronow WS, Yalamanchili K, Peterson SJ, Frishman WH, Babu S. Association of ankle-brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. Cardiology 2005; 103(3):158–160
4 Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. J Clin Invest 1975;56(3):624–632
5 Majerus PW. Arachidonate metabolism in vascular disorders. J Clin Invest 1983;72(5):1521–1525
6 Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl): 199S–233S
7 Wong PF, Chong LY, Mikhailidis DP, Robless P, Stansby G. Antiplatelet agents for intermittent claudication. Cochrane Database Syst Rev 2011;11(11):CD001272
8 Hollopeter G, Jantzen HM, Vincent D, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. Nature 2001;409(6817):202–207
9 Biondi-Zoccai G, Lotrionte M, Agostoni P, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol 2011; 150(3):325–331
10 Nawarskas JJ, Clark SM. Ticagrelor: a novel reversible oral antiplatelet agent. Cardiol Rev 2011;19(2):95–100
11 Aster RH. Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. Chest 2005;127(2, Suppl):53S–59S
12 Born G, Patrono C. Antiplatelet drugs. Br J Pharmacol 2006;147 (Suppl 1):S241–S251
13 Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143(1-2):1–13
14 Weyrich AS, Denis MM, Kuhlmann-Eyre JR, et al. Dipyridamole selectively inhibits inflammatory gene expression in platelet-monocyte aggregates. Circulation 2005;111(5):633–642
15 Katakami N, Kim YS, Kawamori R, Yamasaki Y. The phosphodiesterase inhibitor cilostazol induces regression of carotid atherosclerosis in subjects with type 2 diabetes mellitus: principal results of the Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) study: a randomized trial. Circulation 2010;121(23): 2584–2591
16 Kambayashi J, Liu Y, Sun B, Shakur Y, Yoshitake M, Czerwiec F. Cilostazol as a unique antithrombotic agent. Curr Pharm Des 2003;9(28):2289–2302
17 Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. Br J Haematol 2008;141(6):757–763
18 Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–1151
19 Shammas NW. Complications in peripheral vascular interventions: emerging role of direct thrombin inhibitors. J Vasc Interv Radiol 2005;16(2 Pt 1):165–171
20 Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–891
21 Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–992
22 Hirsh J, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 1992;102(4, Suppl):337S–351S
23 Robless P, Okonko D, Mikhailidis DP, Stansby G. Dextran 40 reduces in vitro platelet aggregation in peripheral arterial disease. Platelets 2004;15(4):215–222
24 Dörffler-Melly J, Koopman MM, Prins MH, Büller HR. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. Cochrane Database Syst Rev 2005;(1):CD002071
25 Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. J Clin Invest 1968;47 (9):2169–2180
26 Goldhaber SZ, Manson JE, Stampfer MJ, et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. Lancet 1992;340(8812):143–145
27 Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. Lancet 2000;355 (9201):346–351
28 Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e669S–690S
29 Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001–2015
30 Kowalczyk M, Banach M, Mikhailidis DP, Hannam S, Rysz J. Ticagrelor—a new platelet aggregation inhibitor in patients with acute coronary syndromes. An improvement of other inhibitors? Med Sci Monit 2009;15(12):MS24–MS30
31 Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011;57(6): 672–684
32 Bhatt DL. Prasugrel in clinical practice. N Engl J Med 2009;361 (10):940–942
33 Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;120 (25):2577–2585
34 Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos 2010;38(1):92–99
35 Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. J Am Coll Cardiol 2011;57(11):1251–1263
36 Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination versus aspirin alone after lower limb angioplasty. Br J Surg 2005;92(2):159–165
37 Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Clopidogrel has no effect on D-dimer and thrombin-antithrombin III levels in patients with peripheral arterial disease undergoing peripheral percutaneous transluminal angioplasty. J Vasc Surg 2005; 42(2):252–258

38 Milani RV. Antiplatelet therapy after endovascular intervention: does combination therapy really work and what is the optimum duration of therapy? Catheter Cardiovasc Interv 2009;74(Suppl 1): S7–S11
39 Visonà A, Tonello D, Zalunardo B, et al. Antithrombotic treatment before and after peripheral artery percutaneous angioplasty. Blood Transfus 2009;7(1):18–23
40 Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Surg 1998;27 (2):267–274, discussion 274–275
41 Shinohara Y, Katayama Y, Uchiyama S, et al; CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol 2010;9(10):959–968
42 What is peripheral arterial disease? National Heart Lung and Blood Institute. 2012http://www.nhlbi.nih.gov/health/health-topics/topics/pad/printall-index.html. Accessed June 29, 2012.
43 Arfvidsson B, Lundgren F, Drott C, Scherstén T, Lundholm K. Influence of coumarin treatment on patency and limb salvage after peripheral arterial reconstructive surgery. Am J Surg 1990; 159(6):556–560
44 Sarac TP, Huber TS, Back MR, et al. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. J Vasc Surg 1998;28(3):446–457
45 Johnson WC, Williford WO; Department of Veterans Affairs Cooperative Study #362. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. J Vasc Surg 2002;35(3):413–421
46 Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. Cochrane Database Syst Rev 2011;(6):CD000536
47 Thompson JF, Mullee MA, Bell PR, et al. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group study. Eur J Vasc Endovasc Surg 1996;12(1):86–90
48 Gram J, Mercker S, Bruhn HD. Does protamine chloride neutralize low molecular weight heparin sufficiently? Thromb Res 1988; 52(5):353–359
49 van Veen JJ, Maclean RM, Hampton KK, et al. Protamine reversal of low molecular weight heparin: clinically effective? Blood Coagul Fibrinolysis 2011;22(7):565–570
50 Norgren L; Swedish EnoxaVasc Study Group. Can low molecular weight heparin replace unfractionated heparin during peripheral arterial reconstruction? An open label prospective randomized controlled trial. J Vasc Surg 2004;39(5): 977–984
51 Hess H, Mietaschk A, Deichsel G. Drug-induced inhibition of platelet function delays progression of peripheral occlusive arterial disease. A prospective double-blind arteriographically controlled trial. Lancet 1985;1(8426):415–419
52 Collaborative overview of randomised trials of antiplatelet therapy—II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. BMJ 1994;308(6922):159–168
53 Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354(16): 1706–1717
54 Belch JJ, Dormandy J, Biasi GM, et al; CASPAR Writing Committee. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg 2010;52(4):825–833, e1–e2
55 Smout JD, Mikhailidis DP, Shenton BK, Stansby G. Combination antiplatelet therapy in patients with peripheral vascular bypass grafts. Clin Appl Thromb Hemost 2004;10(1):9–18
56 Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26(3):517–538
57 Katz SG, Kohl RD. Does dextran 40 improve the early patency of autogenous infrainguinal bypass grafts? J Vasc Surg 1998;28(1): 23–26, discussion 26–27
58 Rooke TW, Hirsch AT, Misra S, et al; American College of Cardiology Foundation; American Heart Association; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. Catheter Cardiovasc Interv 2012;79(4): 501–531