# A Structured Review of Antithrombotic Therapy in Peripheral Artery Disease With a Focus on Revascularization

## A TASC (InterSociety Consensus for the Management of Peripheral Artery Disease) Initiative

**ABSTRACT:** Peripheral artery disease affects >200 million people worldwide and is associated with significant limb and cardiovascular morbidity and mortality. Limb revascularization is recommended to improve function and quality of life for symptomatic patients with peripheral artery disease with intermittent claudication who have not responded to medical treatment. For patients with critical limb ischemia, the goals of revascularization are to relieve pain, help wound healing, and prevent limb loss. The baseline risk of cardiovascular and limb-related events demonstrated among patients with stable peripheral artery disease is elevated after revascularization and related to atherothrombosis and restenosis. Both of these processes involve platelet activation and the coagulation cascade, forming the basis for the use of antiplatelet and anticoagulant therapies to optimize procedural success and reduce postprocedural cardiovascular risk. Unfortunately, few high-quality, randomized data to support use of these therapies after peripheral artery disease revascularization exist, and much of the rationale for the use of antiplatelet agents after endovascular peripheral revascularization is extrapolated from percutaneous coronary intervention literature. Consequently, guideline recommendations for antithrombotic therapy after lower limb revascularization are inconsistent and not always evidence-based. In this context, the purpose of this structured review is to assess the available randomized data for antithrombotic therapy after peripheral arterial revascularization, with a focus on clinical trial design issues that may affect interpretation of study results, and highlight areas that require further investigation.

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Peripheral artery disease (PAD) commonly refers to atherosclerotic arterial occlusive disease of the lower extremities, which will be the focus of this review.[1] PAD is reported to affect 202 million people worldwide in 2010.[2,3] In an administrative database of >9 million patients in the United States, the prevalence of symptomatic PAD was 10.7% and of critical limb ischemia (CLI) was 1.3%.[4] As a result of a growing proportion of older patients, the prevalence of PAD is rising: between 2000 and 2010, the number of PAD cases increased by 13% in high-income countries and 29% in low- and middle-income countries.[2]

Symptomatic PAD can manifest as atypical, exercise-limiting limb symptoms, intermittent claudication (IC, pain induced by walking and relieved by rest), or chronic CLI (ischemic rest pain or ulceration for >14 days).[5,6] Indications for revascularization in patients with PAD vary according to clinical presentation. In lifestyle-limiting IC unresponsive to medical treatment, revascularization is recommended to improve walking capacity and quality of life.[5,6] In CLI, patients should always be considered for revascularization with the goals of relieving pain, healing ischemic ulcers, and preventing limb loss.[5,6]

Contemporary series demonstrate that ≈20% of lower limb revascularization procedures are performed surgically, and 80% are endovascular.[7,8] Procedures are performed by specialists in vascular surgery, interventional cardiology, interventional radiology, and interventional angiology/vascular medicine. A major limitation of revascularization is restenosis or thrombosis with subsequent failure of the procedure, with mean patency rates of 56% to 77% at 1 year and 39% to 80% at 5 years, depending on revascularization method and location of disease.[6]

In addition to the risk of limb-related events, patients with PAD, who often have more widespread atherosclerosis than patients with coronary artery or cerebrovascular disease,[9] have an increased risk of cardiovascular morbidity and mortality.[10] Recent clinical trial data showed that 11% to 12% of patients with stable, symptomatic PAD suffered cardiovascular death, myocardial infarction (MI), or stroke, and 2% to 4% were hospitalized for acute limb ischemia (ALI) over 36 months of follow-up.[11] After PAD revascularization, corresponding risks are even higher, with reported rates of nonfatal MI, ischemic stroke, or cardiovascular death 36 months after procedure of 14% among patients with IC and 34% among those with CLI.[12] A prior history of peripheral revascularization is a strong predictor of ALI,[13] and compared with patients with stable PAD, those with a history of limb revascularization >30 days before enrollment have a significantly higher risk of MI (adjusted hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.08–1.55) and ALI (adjusted HR, 4.23; 95% CI, 2.86–6.25).[14] These risks are further elevated after repeat limb revascularization, supporting the need for more aggressive secondary prevention measures, including intensive antithrombotic therapy, to prevent recurrent events in this high-risk population.

Despite the greater risk of cardiovascular and limb adverse outcomes in patients with PAD undergoing limb revascularization, high-quality data on antithrombotic therapy in this clinical context are sparse. As a result, recommendations regarding antithrombotic therapy for these patients are based on lower levels of evidence and are inconsistent.[5,6,15–17] The purpose of this structured review is to critically examine the design and results of clinical trials of antithrombotic therapy after peripheral arterial revascularization that provide the current evidence to support practice decisions and guidelines, highlighting gaps in knowledge and areas requiring further investigation. For this review, a comprehensive literature search was conducted to identify and retrieve all relevant published international publications pertaining to antithrombotic therapy in PAD in patients undergoing revascularization (see online-only Data Supplement for details). Given the limitations of observational analyses, only data from randomized trials were included, with the exception of 1 large registry-based study using well-validated data.[12]

## Pathobiology and Mechanisms of Atherothrombosis and Restenosis

Morbidity and mortality in patients with PAD is related to both acute arterial thrombosis and luminal stenosis. Platelets play a central role in acute thrombosis through complex biological pathways.[18] When endothelium or atherosclerotic plaque is disrupted, platelets adhere to subendothelial matrix ligands and to each other, forming a rudimentary plug. A second phase of thrombosis involves platelet activation, an autocrine and paracrine stimulation of redundant platelet receptors, including P2Y12, protease-activated receptors (PAR-1 and PAR-4), and thromboxane receptors (TP$\alpha$ and TP$\beta$). Platelet activation promotes morphological changes and glycoprotein IIb/IIIa receptor expression that further increase platelet adhesion. The latter stages of thrombosis involve activation of the coagulation cascade at the platelet surface, with production of thrombin. Thrombin catalyzes fibrin cross-linking of platelets to stabilize the thrombus and is a potent platelet activator through PAR-1 and PAR-4 stimulation, spurring further platelet adhesion and thrombus propagation. Therefore, acute thrombosis depends on amplified interplay between platelets and coagulation, with thrombin driving the process (Figure 1).[19] Endovascular and surgical techniques disrupt endothelium and atherosclerotic plaques and introduce foreign bodies, all of which may activate platelets and local coagulation factors, initiate atherothrombosis, and result in occlusion.

In contrast with acute thrombosis, mechanisms of arterial restenosis reflect remodeling of the arterial wall and

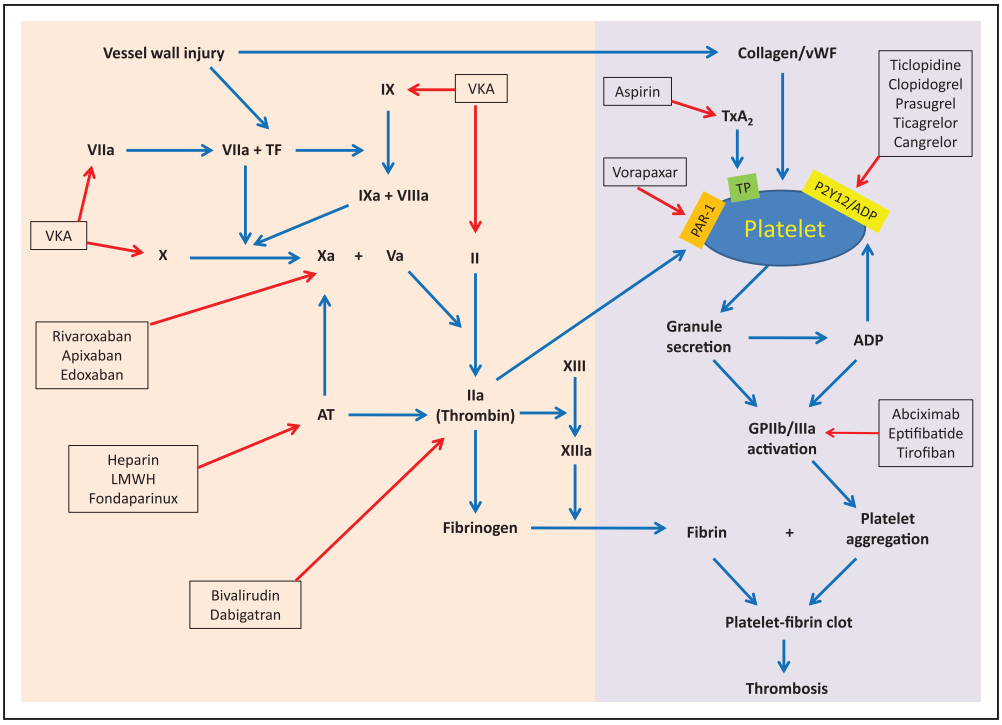


**Figure 1. Pathways of coagulation and platelet aggregation.**
Components of the coagulation cascade and platelet activation and aggregation, which ultimately result in the formation of a platelet-fibrin clot and thrombosis. Various anticoagulant and antiplatelet agents and their targets are also shown. Adapted with permission.[19] ADP indicates adenosine diphosphate; AT, antithrombin; GP, glycoprotein; LMWH, low molecular weight heparin; PAR, protease-activated receptor; TP, thromboxane receptor; $TxA_2$, thromboxane $A_2$; VKA, vitamin K antagonist; and vWF, von Willebrand factor.

depend on the modality of revascularization. Endovascular revascularization with percutaneous transluminal angioplasty induces both short- and long-term changes that promote restenosis. Elastic recoil is common and decreases lumen diameter after angioplasty.[20] Initial lumen narrowing from elastic recoil may promote prostenotic physiological changes and is associated with future restenosis,[21] whereas long-term restenosis after angioplasty is likely mediated by arterial remodeling.[22] Arterial remodeling involves adaptive revision to vessel adventitial composition and is stimulated by endothelial signaling in response to changes in shear stress.[23] Lumen diameter changes from remodeling show a positive correlation with arterial flow, and poor postprocedural flow disturbances can increase lumen-narrowing remodeling.[23]

The use of stents after angioplasty prevents early lumen loss from elastic recoil and minimizes the effects of arterial remodeling. However, stented arteries are subject to restenosis, primarily through subsequent neointimal hyperplasia, a response to endothelial injury and inflammation.[22] Venous grafts are at risk for a similar complication because of endothelial injury,[24] whereas synthetic grafts that do not endothelialize develop flow-limiting intimal hyperplasia in anastomotic regions from disturbed flow caused by differences in compliance between the prosthetic material and native vessel.[25] Endothelial injury, the inciting event in both intimal and neointimal hyperplasia, triggers platelet adherence and disrupts normal endothelial production of antithrombotic prostacyclin and nitrous oxide. Activation of adherent platelets leads to the production of mitogens, such as thrombin, thromboxane $A_2$, and platelet-derived growth factor, which promote proliferation of vascular smooth muscle cells and their migration into the intima. Coagulation cascade activation at the site of endothelial injury may also contribute directly to intimal hyperplasia since disruption of tissue factor stimulation of coagulation attenuates intimal hyperplasia.[26,27]

Intimal hyperplasia causing in-stent and surgical graft restenosis is likely promoted most strongly by smooth muscle cell proliferation and migration, as evidenced by the retardant effects of therapies targeting vascular smooth muscle cells. Stents eluting the drugs paclitaxel and sirolimus, cytotoxic to smooth muscle cells, have shown reduced restenosis rates compared with bare metal stents in coronary and peripheral revascularization.[28,29] Other novel emerging antimitogenic therapeutics further point to a key role of vascular smooth muscle cells.[30,31] The phosphodiesterase-3 inhibitor cilostazol is an antiplatelet drug that appears to have additional inhibitory effects on smooth muscle cell proliferation and stimulatory effects on endothelial cell growth.[31] These pleiotropic effects of cilostazol may underlie its reported benefits in preventing restenosis in peripheral artery stenting.[32,33]

As illustrated, platelet activation and the coagulation cascade are involved in atherothrombosis and restenosis after revascularization, forming the basis for trials of post-procedural antiplatelet and anticoagulant therapies. These mechanisms may also provide insight into future targets to improve outcomes in this population.

## Pharmacology of Antithrombotic Agents

Antithrombotic therapies can be divided into antiplatelet and anticoagulant agents (Figure 1).[18,19] Antiplatelet therapies interrupt platelet activation and aggregation. Aspirin does so by inhibiting cyclooxygenase 1, preventing the formation of thromboxane $A_2$, whereas cilostazol and dipyridamole inhibit phosphodiesterase 3. Ticlopidine prevents platelet aggregation by blocking the platelet surface adenosine diphosphate receptor, and clopidogrel and prasugrel indirectly inhibit the P2Y12 receptor. Direct inhibitors of the P2Y12 receptor include ticagrelor and cangrelor. The antiplatelet effects of vorapaxar are a result of its inhibition of the protease-activated receptor 1, which is involved in thrombin-induced platelet aggregation. Platelet glycoprotein IIb/IIIa receptor inhibition by abciximab, eptifibatide, and tirofiban also prevents platelet aggregation and thrombus formation.

In contrast, anticoagulant agents prevent thrombus formation by interrupting the coagulation cascade (Figure 1).[18,19] Vitamin K antagonists, such as warfarin, phenprocoumon, and dicumarol, inhibit the activation of vitamin K-dependent clotting factors, including factors II, VII, IX, and X, as well as anticoagulant proteins C and S. Rivaroxaban, apixaban, and edoxaban selectively inhibit factor Xa, whereas heparin, low-molecular-weight heparin, and fondaparinux potentiate factor Xa neutralization through activation of antithrombin III, all reducing thrombin formation. Lastly, bivalirudin and dabigatran provide anticoagulant effects by inhibiting thrombin. Studies examining the use of these agents in stable PAD and after peripheral revascularization will be discussed below.

## Clinical Trial Design for Studies of Antithrombotic Therapies After Peripheral Arterial Revascularization

Relative to studies of antithrombotic therapies in acute coronary syndrome or after percutaneous coronary intervention, few randomized trial data support the use of these therapies in patients with PAD with or without revascularization. Furthermore, interpretation of available studies is hindered by multiple and varying limitations of each trial. To inform a critical appraisal of existing data, important components of clinical trial design for a study of antithrombotic therapy after peripheral revascularization are examined.

### *End Points*

Relevant efficacy end points for trials of antithrombotic therapies in PAD revascularization can be broadly categorized into limb-related and systemic outcomes (Figure 2). Limb outcomes may be further categorized into clinical versus surrogate end points. Examples of clinical end points include changes in function and quality of life, as measured by peak treadmill walking time and the Peripheral Artery or Walking Impairment Questionnaires, respectively, or improvement in a patient's clinical stage, as assessed by the Rutherford classification for PAD.[34] Major amputation, repeat limb revascularization for occlusion, and ALI are additional clinically relevant end points. The outcome of major adverse limb events (MALE) is variably defined as a combination of the following components: ALI, thrombectomy or thrombolysis, major amputation, or repeat surgical revascularization of the target limb.[34,35]

In addition to clinical end points, surrogate end points may be used when evaluating limb outcomes in antithrombotic treatment after PAD revascularization.[34] One such surrogate end point is change in ankle-brachial index or toe-brachial index, usually defined as a meaningful difference of ≥0.10. Transcutaneous

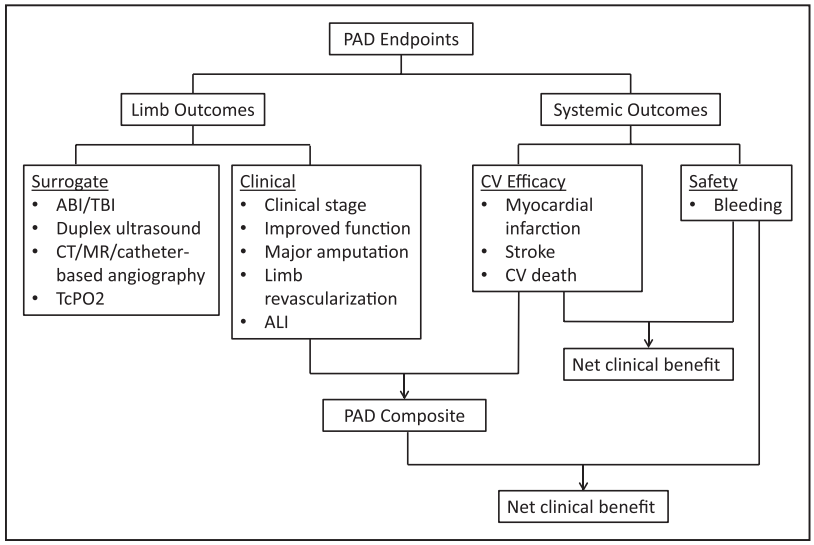


**Figure 2. End points for trials of antithrombotic therapies in PAD revascularization.**
Shown are categories of relevant end points for clinical trials of antithrombotic therapies after peripheral arterial revascularization. ALI indicates acute limb ischemia; CV, cardiovascular; PAD, peripheral artery disease; and $TcPO_2$, transcutaneous oxygen tension.

oxygen content is an end point often used in CLI trials. Measures of vascular patency have also been assessed, including primary (without further intervention) and assisted graft patency and significant target lesion restenosis, defined as a peak systolic velocity ratio of >2.4 by duplex ultrasonography or >50% diameter or >70% area stenosis on computed tomographic, magnetic resonance, or catheter-based angiography. As with the use of all surrogate outcomes, there may or may not be a true correlation with clinical benefit, and therapeutic efficacy on a surrogate outcome may not translate into a true health benefit. However, these end points can provide important information on the mechanism of action and the effect of a drug or device.

Given the high cardiovascular risk associated with PAD, systemic outcomes are an important focus of studies of antithrombotic therapy after limb revascularization. To address this, studies often examine a composite of major adverse cardiac events (MACE), which is typically defined as cardiovascular death, nonfatal MI, or nonfatal stroke. All-cause mortality is another important outcome for this population. Although not typically used for PAD trials, an expanded MACE definition may include additional end points, such as hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure.

It should be noted that many of the early trials of aspirin and other antiplatelet drugs were performed in small populations where the primary end point of the trial was procedural patency. In these studies, MACE was not the primary end point but was captured as an unadjudicated adverse event. Assessments of MACE in this context are unreliable with respect to event estimates and study drug treatment effects on these events and highlight the importance of prospective definition and collection and blinded adjudication of major events of interest, including MACE, MALE, and major bleeding.

The primary systemic safety outcome for trials of antithrombotic therapies is major bleeding, an issue particularly important after PAD revascularization, which is associated with its own procedural bleeding risk. The most widely used bleeding classification systems are the Thrombolysis in Myocardial Infarction, Bleeding Academic Research Consortium, and International Society on Thrombosis and Haemostasis.[36] Specific to patients with PAD undergoing revascularization, procedure-related bleeding events that are serious enough to require procedural intervention to stop the bleeding are of interest to both clinicians and regulatory agencies. To date, many of the trials of antithrombotic therapies in PAD have captured bleeding as unadjudicated adverse events or have adjudicated prospectively defined bleeds but have not used a defined bleeding scale; few have adjudicated bleeding as a primary safety outcome according to a standard classification system (Tables 1–3).[11,37–73]

To balance the potential risks and benefits of antithrombotic therapies, the concept of net clinical benefit has been applied. The net clinical benefit measure tries to quantify the tradeoff between the experimental treatment effect on reduced risk of atherothrombotic or thrombotic efficacy versus increased risk of bleeding associated with antithrombotic medications.[74] The simplest approach assumes that efficacy and safety events are of equal clinical importance and calculates the numeric difference between efficacy events avoided and bleeding events caused by the treatment. In situations where end points are of different clinical importance, a weighted sum can be calculated to account for these differences. A further refinement is a bivariate approach where unweighted efficacy and safety events are evaluated in a 2-by-2 bivariate space, allowing for net clinical benefit to be compared between trials and drugs in a similar class.[74] Although net clinical benefit has not yet been used as a primary outcome in clinical trials of antithrombotic therapies in patients with PAD, this approach might provide additional information to help providers optimize treatments for this high-risk population.

### Study Population

The choice of study population is another key component to successful clinical trial design. Most randomized assessments of antithrombotic therapy for PAD have been limited by small sample size as well as heterogeneity in study population and end points, especially in the post-revascularization setting (Tables 1–3). To date, few large-scale trials enrolling a primary PAD population have been completed, and these have focused on patients with stable PAD.[37,38] Although some large antithrombotic therapy trials have included PAD as an inclusion criterion and performed prespecified analyses of patients with PAD,[11,13,39,40] other data have come from post hoc subgroup analyses of patients with PAD at the time of randomization;[41] all of these analyses are hypothesis-generating only.

### Comparator and Background Treatment

Another important component of clinical trial design is selection of a comparator treatment. Comparator treatments may include a placebo used in the early trials of aspirin or active treatment and should be chosen to address true uncertainties and explore treatments for which there is clinical equipoise. Although comparison of a new antithrombotic drug to placebo may be performed to demonstrate efficacy, that design would require that both groups received standard background therapy (eg, aspirin). When the trial design uses an active comparator, the control arm should not use an active comparator that is either known to be less effective than the standard of care or at a less effective dose because that can lead to comparator bias, biasing a trial toward a positive result. Conversely, selection of a potent active comparator may reduce the likelihood of a positive trial but may definitively answer a clinical uncertainty. In this situation, a noninferiority design may be used. Thus, comparator treatment selection can significantly affect trial results in either direction.

**Table 1. Antithrombotic Therapy for Stable PAD**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Primary Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| Meta-analyses of various antiplatelet agents | | | | | | |
| Antithrombotic Trialists' Collaboration (1994)[56] | Intermittent claudication subgroup | 400 | Antiplatelet therapy vs placebo | Vascular patency | Bleeding* | Efficacy: odds reduction, 64% (standard deviation, 18%) |
| Antithrombotic Trialists' Collaboration (2002)[42] | Intermittent claudication subgroup | 6263 | Antiplatelet therapy vs placebo | Vascular death, MI, or stroke | Bleeding | Efficacy: odds reduction, 23% (standard error, 9%) |
| Aspirin | | | | | | |
| CLIPS (2007)[43] | Fontaine stage I or II PAD | 366 | Aspirin vs placebo<br>Antioxidant vs placebo (2×2) | Validated vascular death, MI, or stroke | Bleeding | Enrollment stopped early.<br>Efficacy: HR, 0.35 (95% CI, 0.15–0.82)<br>Safety: 2.2% vs 0% (*P* not calculated) |
| POPADAD (2008)[44] | Diabetes mellitus and asymptomatic† PAD | 1276 | Aspirin vs placebo | Adjudicated death from coronary heart disease or stroke, nonfatal MI or stroke, or above-ankle amputation for critical limb ischemia | Bleeding | Efficacy: HR, 0.98 (95% CI, 0.76–1.26) |
| Berger (2009)[45] | Meta-analysis of small trials mainly evaluating patency | 5269 | Aspirin with or without dipyridamole vs placebo | Cardiovascular death, MI, or stroke | Major bleeding as defined in each study | Efficacy: HR, 0.88 (95% CI, 0.76–1.04)<br>Safety: RR, 0.99 (95% CI, 0.66–1.50) |
| Aspirin for Asymptomatic Atherosclerosis Trialists (2010)[37] | Asymptomatic PAD† | 3350 | Aspirin vs placebo | Adjudicated fatal or nonfatal coronary event or stroke or revascularization | Adjudicated major hemorrhage requiring admission† | Efficacy: HR, 1.03 (95% CI, 0.84–1.27)<br>Safety: HR, 1.71 (95% CI, 0.99–2.97) |
| Clopidogrel | | | | | | |
| CAPRIE (1996)[40] | Recent MI, recent ischemic cerebrovascular accident, or symptomatic PAD | 19185 | Clopidogrel vs aspirin | Validated vascular death, MI, or ischemic stroke | Bleeding | Efficacy: RR, 0.91 (95% CI, 0.84–0.97) |
| | PAD subgroup | 6452 | Clopidogrel vs aspirin | Validated vascular death, MI, or ischemic stroke | Bleeding | Efficacy: RR, 0.76 (95% CI, 0.64-0.91) |
| CHARISMA (2006)[46] | Coronary artery disease, cerebrovascular disease, symptomatic PAD, or atherosclerotic risk factors | 15603 | Clopidogrel plus aspirin vs aspirin alone | Adjudicated cardiovascular death, MI, or stroke | Adjudicated GUSTO severe bleeding | Efficacy: RR, 0.93 (95% CI, 0.83 to 1.05)<br>Safety: RR, 1.25 (95% CI, 0.97–1.61) |

(*Continued*)

**Table 1. Continued**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Primary Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| CHARISMA (2009)[39] | PAD subgroup | 3096 | Clopidogrel plus aspirin vs aspirin alone | Adjudicated cardiovascular death, MI, or stroke | Adjudicated GUSTO severe bleeding | Efficacy: HR, 0.85 (95% CI, 0.66–1.08)<br>Safety: RR, 0.97 (95% CI, 0.56–1.66) |
| Vorapaxar | | | | | | |
| TRACER (2012)[50] | Non-ST-elevation acute coronary syndrome plus ≥1 of the following: ≥55 y of age; prior MI, percutaneous coronary intervention, or coronary artery bypass grafting; diabetes mellitus; or PAD | 12 944 | Vorapaxar vs placebo | Adjudicated cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization | Adjudicated GUSTO moderate or severe bleeding | Efficacy: HR, 0.92 (95% CI, 0.85–1.01)<br>Safety: HR, 1.35 (95% CI, 1.16–1.58) |
| TRACER (2014)[51] | PAD subgroup | 936 | Vorapaxar vs placebo | Adjudicated cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization | Adjudicated GUSTO moderate or severe bleeding | Efficacy: HR, 0.85 (95% CI, 0.64–1.13)<br>Safety: HR, 1.47 (95% CI, 0.89–2.45) |
| TRA 2°P-TIMI 50 (2012)[52] | Prior MI, ischemic stroke, or PAD | 26 449 | Vorapaxar vs placebo | Adjudicated cardiovascular death, MI, or stroke | Adjudicated GUSTO moderate or severe bleeding | Efficacy: HR, 0.87 (95% CI, 0.80–0.94)<br>Safety: HR, 1.66 (95% CI, 1.43–1.93) |
| TRA 2°P-TIMI 5 (2013)[11] | PAD subgroup | 3787 | Vorapaxar vs placebo | Adjudicated cardiovascular death, MI, or stroke | Adjudicated GUSTO moderate or severe bleeding | Efficacy: HR, 0.94 (95% CI, 0.78–1.14)<br>Safety: HR, 1.62 (95% CI, 1.21–2.18) |
| Ticagrelor | | | | | | |
| PLATO (2009)[47] | Acute coronary syndrome | 18 624 | Ticagrelor vs clopidogrel | Adjudicated vascular death, MI, or stroke | Adjudicated PLATO major bleeding | Efficacy: HR, 0.84 (95% CI, 0.77–0.92)<br>Safety: HR, 1.04 (95% CI, 0.95–1.13) |
| PLATO (2015)[48] | PAD subgroup | 1144 | Ticagrelor vs clopidogrel | Adjudicated vascular death, MI, or stroke | Adjudicated PLATO major bleeding | Efficacy: HR, 0.85 (95% CI, 0.64–1.11)<br>Safety: HR, 0.81 (95% CI, 0.59–1.10) |
| PEGASUS-TIMI 54 (2015)[49] | Prior MI within past 1–3 y | 21 162 | Ticagrelor plus aspirin vs aspirin alone | Adjudicated cardiovascular death, MI, or stroke | Adjudicated TIMI major bleeding | Efficacy: 90-mg dose: HR, 0.85 (95% CI, 0.75–0.96)<br>60-mg dose: HR, 0.84 (95% CI, 0.74–0.95)<br>Safety: 90-mg dose: HR, 2.69 (95% CI, 1.96–3.70) |
| PEGASUS-TIMI 54 (2015)[49] (Continued) | | | | | | 60-mg dose: HR, 2.32 (95% CI, 1.68–3.21) |

(*Continued*)

**Table 1. Continued**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Primary Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| PEGASUS-TIMI 54 (2016)[41] | PAD subgroup | 1143 | Ticagrelor plus aspirin vs aspirin alone | Adjudicated cardiovascular death, MI, or stroke | Adjudicated TIMI major bleeding | Efficacy: 90-mg dose: HR, 0.81 (95% CI, 0.57-1.15)<br>60-mg dose: HR, 0.69 (95% CI, 0.47-0.99)<br>Safety: 90-mg dose: HR, 1.46 (95% CI, 0.39-5.43)<br>60-mg dose: HR, 1.18 (95% CI, 0.29-4.71) |
| EUCLID (2016)[38] | Stable PAD | 13 800 | Ticagrelor vs clopidogrel | Adjudicated cardiovascular death, MI, or ischemic stroke | Adjudicated TIMI major bleeding | Efficacy: HR, 1.02 (95% CI, 0.92–1.13)<br>Safety: HR, 1.10 (95% CI, 0.84–1.43) |
| Anticoagulation | | | | | | |
| WAVE (2007)[53] | PAD or carotid artery disease | 2161 | Warfarin or acenocoumarol vs aspirin, ticlopidine, or clopidogrel | Coprimary 1: Adjudicated cardiovascular death, MI, or stroke<br>Coprimary 2: Adjudicated cardiovascular death, MI, stroke, or urgent peripheral or coronary artery intervention for severe ischemia | Adjudicated bleeding† | Efficacy: Coprimary 1: RR, 0.92 (95% CI, 0.73–1.16)<br>Coprimary 2: RR, 0.91 (95% CI, 0.74–1.12)<br>Safety: RR, 3.41 (95% CI, 1.84–3.65) |
| ROCKET-AF (2011)[54] | Nonvalvular atrial fibrillation with moderate to high stroke risk | 14 264 | Rivaroxaban vs warfarin | Adjudicated stroke and systemic embolism | Adjudicated bleeding† | Efficacy: HR, 0.79 (95% CI, 0.66–0.96)<br>Safety: HR, 1.03 (95% CI, 0.96–1.11) |
| ROCKET-AF (2013)[55] | PAD subgroup | 839 | Rivaroxaban vs warfarin | Adjudicated stroke and systemic embolism | Adjudicated bleeding† | Efficacy: HR, 1.19 (95% CI, 0.63–2.22)<br>Safety: HR, 1.40 (95% CI, 1.06–1.86) |

Asymptomatic PAD is evidence of occlusive atherosclerosis in the limb based on an abnormal ankle-brachial index without symptoms of vascular disease. CAPRIE indicates Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CI, confidence interval; CLIPS, Critical Leg Ischaemia Prevention Study; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; TIMI, Thrombolysis in Myocardial Infarction; TRA 2°P-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50; and WAVE, Warfarin Antiplatelet Vascular Evaluation.

*Bleeding assessed by a variety of measures, including ascertainment of adverse events or various bleeding scores without clearly defined adjudication parameters.

†Prospectively defined and collected bleeding events not assessed with a defined bleeding scale.

## *Summary*

Multiple issues should be considered in the design and interpretation of data from studies of antithrombotic therapy in PAD revascularization, and variations in design components have been listed in Figure 3. Ideally, a study of antithrombotic treatment after PAD revascularization would enroll a primary PAD population, include a composite adjudicated MACE and MALE primary efficacy end point, and assess a primary safety end point of adjudicated major bleeding events according to a defined

bleeding scale as well as bleeding requiring procedural intervention for hemostasis.

## Antithrombotic Therapy for Medical Management of Stable PAD

Most data for antithrombotic therapy use in the PAD population have come from studies of patients with stable PAD (Table 1).

### *Aspirin*

Although meta-analyses have shown that antiplatelet agents reduce the risk of vascular death, MI, and stroke by ≈25% among patients with symptomatic coronary and cerebrovascular disease,[42,75] randomized trials have not consistently demonstrated efficacy of aspirin for reduction of cardiovascular events in stable PAD. A meta-analysis by the Antithrombotic Trialists' Collaboration found a 22% odds reduction for cardiovascular events among patients with symptomatic PAD treated with antiplatelet therapy.[42] However, this study included antiplatelet agents other than aspirin or clopidogrel and is based on older data where standard background therapies were not available (eg, statins). More recently, in a small trial of aspirin versus placebo in patients with Fontaine stage I-II PAD, aspirin reduced vascular death, MI, or stroke, but this trial stopped enrollment early after randomizing only 18% of the intended population.[43] Another placebo-controlled trial in patients with diabetes mellitus and asymptomatic PAD found no benefit for aspirin in reducing ischemic cardiovascular events or major amputation for CLI.[44] In a meta-analysis of 18 trials involving 5269 patients with PAD, aspirin (given in a wide range of doses with or without dipyridamole) versus placebo resulted in a nonsignificant relative risk reduction of 12% for cardiovascular death, MI, or stroke.[45] Although MACE was the primary outcome of this meta-analysis, only 2 of the included trials evaluated MACE as the primary end point; the majority of trials assessed MACE as secondary end points or safety events. The largest randomized placebo-controlled trial of aspirin in 3350 asymptomatic patients with PAD found no efficacy of aspirin for the prevention of coronary events, stroke, or revascularization (HR, 1.03; 95% CI, 0.84–1.27).[37] An observational, population-based study of 18 742 revascularized patients with PAD in the Swedvasc Registry demonstrated that antiplatelet therapy, most commonly aspirin, was prescribed at admission to 73% of patients but was not associated with cardiovascular protection.[12] However, this study was limited by lack of randomization and control of confounding.

### *Clopidogrel*

In the CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events),[40] clopidogrel conferred an 8.7% relative risk reduction for vascular death, MI, or ischemic stroke compared with aspirin among patients with recent MI, recent ischemic stroke, or symptomatic PAD. The risk reduction with clopidogrel versus aspirin was greater among the PAD subgroup (relative risk [RR], 0.76; 95% CI, 0.64–0.91).[40] Bleeding in this study was assessed as an adverse event. These data led to approval of clopidogrel by the US Food and Drug Administration for use in stable PAD 20 years ago, and clopidogrel as an alternative to aspirin monotherapy is now a Class I, Level of Evidence A recommendation for patients with symptomatic PAD.[5]

The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) in patients with established atherosclerotic disease or atherosclerotic risk factors showed that aspirin plus clopidogrel versus aspirin alone resulted in a nonsignificant 7.1% risk reduction in the primary end point of cardiovascular death, MI, or ischemic stroke.[49] In a CHARISMA post hoc analysis of 3096 patients with PAD, the primary end point occurred in 7.6% of the clopidogrel plus aspirin group and in 8.9% of the aspirin-only group (HR, 0.85; 95% CI, 0.66–1.08).[39] Although rates of severe, fatal, or moderate bleeding did not differ between treatment arms, minor bleeding was increased with clopidogrel plus

| | Ideal | Less than ideal | Suboptimal |
|---|---|---|---|
| Study population | Exclusively PAD | PAD as part of inclusion criteria and as a pre-specified subgroup | Post-hoc subgroup analysis of patients with PAD at randomization |
| Primary efficacy endpoint | Adjudicated MACE and MALE | Adjudicated MACE, MALE as adverse events | MACE and MALE collected as adverse events |
| Primary safety endpoint | Adjudicated major bleeds according to defined bleeding scale and bleeds of special interest (procedural bleeds or those requiring an additional procedure to stop bleeding) | Adjudicated major bleeds according to defined bleeding scale | Bleeds collected as adverse events |

**Figure 3. Classification of components of PAD trials evaluating antithrombotic therapies after revascularization.**
Examples of ideal, less than ideal, and suboptimal components of trial design related to the study population, primary efficacy end point, and primary safety end point. MACE indicates major adverse cardiac events; MALE, major adverse limb events; and PAD, peripheral artery disease.




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aspirin (odds ratio [OR], 1.99; 95% CI, 1.69–2.34). Overall, CHARISMA does not support the use of dual antiplatelet therapy (DAPT) in stable, symptomatic PAD.

### Ticagrelor

In the PLATO trial (Platelet Inhibition and Patient Outcomes),[47] ticagrelor as compared with clopidogrel significantly reduced MACE (HR, 0.84; 95% CI, 0.77–0.92) without an increase in major bleeding in patients with acute coronary syndrome. This benefit was numerically similar among the subgroup with PAD (HR, 0.85; 95% CI, 0.64–1.11).[48] In a more recent trial studying ticagrelor plus aspirin versus aspirin alone in patients with prior MI,[49] a subgroup analysis of 1145 patients with PAD demonstrated an absolute risk reduction for cardiovascular death, MI, or stroke with ticagrelor of 4.1%, corresponding to a number needed to treat of 25.[41] The absolute excess of major bleeding was 0.12% (number needed to harm of 834). In this study, ticagrelor significantly reduced the risk of adjudicated MALE, defined as ALI or peripheral revascularization for ischemia (HR, 0.65; 95% CI, 0.44–0.95). An important distinction of this subgroup is that they had both symptomatic coronary disease and PAD.

The EUCLID trial (Examining Use of Ticagrelor in PAD) evaluated ticagrelor versus clopidogrel in 13885 patients with symptomatic PAD.[38] Patients were enrolled from 2 major subgroups: those with a prior lower extremity revascularization (56.7%) and those with a low ankle-brachial index (43.3%). The primary efficacy end point was a composite of cardiovascular death, MI, or ischemic stroke, and the primary safety end point was major bleeding. The primary efficacy end point had a hazard ratio of 1.02 (95% CI, 0.92–1.13; *P*=0.65), and major bleeding had an HR of 1.10 (95% CI, 0.84–1.43; *P*=0.49). The first-ordered secondary end point was the primary end point plus ALI, and that had a hazard ratio of 1.02 (95% CI, 0.92–1.12). Thus, ticagrelor had no benefit over clopidogrel in preventing major cardiovascular or limb events. Patients with a prior revascularization had a risk of ALI of 2.5% compared with 0.6% in patients enrolled based on an abnormal ankle-brachial index. Ticagrelor was not superior to clopidogrel in preventing cardiac or limb events in the prior revascularization subgroup, reflecting the overall results of the trial.

### Vorapaxar

Vorapaxar was studied in high-risk patients with non-ST-segment elevation acute coronary syndromes.[50] Although the trial was terminated early for safety because of bleeding, the target number of primary end points had already accrued by that time, and vorapaxar added to standard therapy did not reduce cardiovascular death, MI, or stroke. In the PAD subgroup, rates of the primary MACE end point were similar in vorapaxar and placebo groups, although there were numerically fewer peripheral revascularization procedures (8.1% versus 9.0%, *P*=0.16) and lower extremity amputations (0.9% versus 1.5%, *P*=0.11).[51] In contrast with the findings in acute coronary syndrome, vorapaxar significantly reduced MACE compared with placebo (HR, 0.87; 95% CI, 0.80–0.94) in patients with stable atherosclerosis, including a history of MI, ischemic stroke, or PAD, although at a cost of increased bleeding.[52] Among the symptomatic PAD subgroup (n=3787), the primary end point was not significantly different with vorapaxar (HR, 0.94; 95% CI, 0.78–1.14).[11] However, vorapaxar reduced the rate of first ALI by 41% (HR, 0.58; 95% CI, 0.39–0.86) and total ALI events by 41% (RR, 0.59; 95% CI, 0.38–0.93).[13] In that same report, vorapaxar also reduced the need for urgent and elective lower extremity revascularizations.

### Anticoagulation

The WAVE trial (Warfarin Antiplatelet Vascular Evaluation) randomized 2161 patients with PAD to oral anticoagulation plus antiplatelet therapy or antiplatelet therapy alone to prevent MACE.[53] After 35 months, there were no differences in MACE (RR, 0.92; 95% CI, 0.73–1.16). Life-threatening bleeding was more common in the warfarin group (RR, 3.41; 95% CI, 1.84–6.35). Thus, full-dose, systemic anticoagulation is harmful in stable PAD and marked by excess bleeding. Rivaroxaban versus warfarin was examined in patients with nonvalvular atrial fibrillation at moderate-high risk of stroke.[54] In a subgroup analysis of patients with baseline PAD, full-dose rivaroxaban did not reduce stroke or systemic embolism compared with warfarin (HR, 1.19; 95% CI, 0.63–2.22) but increased bleeding (HR, 1.40; 95% CI, 1.06–1.86).[55]

## Antithrombotic Therapy After Endovascular Peripheral Revascularization

Peripheral endovascular interventions damage the endothelium, which can lead acutely to thrombosis or longer term restenosis. The goal of post-procedural antithrombotic therapy is to promote efficacy of revascularization and reduce systemic outcomes, including MACE, while minimizing the inherent bleeding risk.

### Extrapolations From Coronary Artery Disease

The use of antiplatelet therapies in patients with stable and acute manifestations of coronary artery disease undergoing percutaneous coronary intervention is mostly evidence-based, and clear recommendations guiding their use exist.[76,77] The benefit of aspirin in acute coronary syndrome was well established with a placebo-controlled trial,[78] and aspirin has since been the cornerstone of antiplatelet therapy for acute coronary syndrome and, by default, percutaneous coronary intervention. Currently, treatment with DAPT with aspirin and a P2Y12 inhibitor is recommended after percutaneous coronary intervention.[76,77] Guidelines for the duration of DAPT vary according to clinical presentation, stent type, and whether procedural success was achieved.[76–78] Clopidogrel has been the most frequently used P2Y12 inhibitor after percutaneous coronary interven-

tion, but its efficacy has been questioned in certain populations,[79,80] and newer P12Y12 inhibitors have a more consistent effect on platelet inhibition.[81] Improved stent platforms may be safer than previous device generations and are associated with significant reductions in thrombotic events.[82] In addition, randomized trials suggest no increased risk of thrombosis after 3 to 6 months of DAPT in patients treated primarily with newer drug-eluting stents.[83–85] Consequently, recommendations favoring a minimum of DAPT therapy for 1 year in patients undergoing elective percutaneous coronary intervention are now being challenged.[78]

In contrast with percutaneous coronary intervention, evidence for medical therapy after peripheral endovascular treatment is sparse (Table 2), and current antiplatelet use after peripheral revascularization is based on the coronary literature. Clinical trials of peripheral endovascular devices, such as atherectomy,[86] stents,[87] covered scaffolds,[88] and drug-coated balloons,[89] empirically included use of variable durations of DAPT after procedure in their protocols without supporting peripheral endovascular-specific data. Based on the coronary literature as well as the use of DAPT in these device trials, many operators use DAPT after peripheral procedures in their clinical practice.[90] Despite similarities between percutaneous interventions in coronary and peripheral arteries, PAD patients have diminished responses to DAPT and increased platelet reactivity compared with patients with coronary artery disease.[91] In light of these physiological differences, inferring benefit of antithrombotic therapies after peripheral artery intervention from the coronary literature may be flawed.

### Aspirin

Although aspirin is widely used after peripheral artery intervention, the effect of aspirin versus placebo after peripheral angioplasty has only been studied in 2 small randomized trials.[57] Both studies, which combined aspirin plus dipyridamole, were evaluated in the most recent Cochrane meta-analysis evaluating antiplatelet and anticoagulant drugs for prevention of restenosis or reocclusion after peripheral endovascular therapy,[57] which included 3529 patients from 22 trials. In this review, no reduction in restenosis or reocclusion with aspirin plus dipyridamole versus placebo was found (OR, 0.69; 95% CI, 0.44–1.10). At 6 months after intervention, a significant reduction in reocclusion was found for high-dose aspirin plus dipyridamole but not in combination with low-dose aspirin. At 12 months after intervention, no statistically significant difference in restenosis or reocclusion was detected for any of the following comparisons: high- versus low-dose aspirin, aspirin plus dipyridamole versus vitamin K antagonists, or clopidogrel and aspirin versus low-molecular-weight heparin plus warfarin. Compared with aspirin alone, low-molecular-weight heparin plus aspirin significantly decreased occlusion/restenosis (by ≤85%) in patients with CLI but not in patients with IC, and batroxobin plus aspirin reduced restenosis in patients with diabetes mellitus.[57] Data on bleeding and other potential gastrointestinal side effects were not consistently reported, although some evidence suggested that high-dose aspirin increased gastrointestinal side effects compared with low-dose aspirin. It should be noted that most of the individual trials were generally small, the risk of bias was often unclear because of limitations in reporting, and only 3 included trials were placebo-controlled.

### Clopidogrel

An attempt was made to evaluate the role of DAPT with clopidogrel and aspirin versus aspirin alone in patients undergoing infrainguinal endovascular intervention in the CAMPER trial (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization), but unfortunately this trial was halted prematurely because of poor enrollment (William R. Hiatt, MD, personal communication, 2016). More recently, another trial randomized 80 patients to clopidogrel plus aspirin versus aspirin alone after femoropopliteal endovascular intervention and found a benefit for DAPT in reducing target lesion revascularization at 6 months (5% versus 20%, $P$=0.04).[58] However, primary events were not adjudicated, and bleeding events were not reported. Clopidogrel was stopped at 6 months, and the benefit did not persist at 12-month follow-up (25% versus 32.4%, $P$=0.35). However, this evidence is not sufficient to support prolonged DAPT with clopidogrel plus aspirin.

### Cilostazol

The effect of cilostazol in patients undergoing peripheral endovascular interventions has been studied in several small randomized trials. Among 127 patients undergoing femoropopliteal endovascular intervention randomized to cilostazol plus aspirin versus ticlopidine plus aspirin, cilostazol significantly improved unadjudicated vascular patency at 36 months following the procedure (OR, 0.40; 95% CI, 0.19–0.83).[59] Bleeding outcomes were not reported. In another trial of 78 patients treated endovascularly for femoropopliteal lesions, cilostazol plus aspirin versus aspirin alone improved freedom from the primary outcome of target vessel revascularization with no difference in major bleeding.[60] The STOP-IC trial (Sufficient Treatment of Peripheral Intervention by Cilostazol) randomized 200 patients undergoing femoropopliteal endovascular intervention to cilostazol plus aspirin versus aspirin alone and found a significant reduction in 12-month angiographic restenosis (OR 0.26; 95% CI, 0.13-0.53) with cilostazol.[61] Bleeding outcomes were not reported.

### Anticoagulation

The results of a recent randomized trial to assess the efficacy and safety comparing edoxaban to clopidogrel on a background of aspirin therapy was presented in abstract form but has not yet been published (Frans L. Moll, MD, PhD, unpublished data, 2015). The trial included 203 patients who underwent femoropopliteal endovascular treatment with or without available stents. The primary efficacy end point was adjudicated restenosis or reocclusion, and





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**Table 2. Antithrombotic Therapy After Endovascular Revascularization for Peripheral Arterial Disease**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| Meta-analyses of various antiplatelet agents | | | | | | |
| Antithrombotic Trialists' Collaboration (1994)[56] | Peripheral angioplasty subgroup | 391 | Antiplatelet therapy vs placebo | Vascular patency | Bleeding* | Efficacy: odds reduction 47% (standard deviation, 25%) |
| Antithrombotic Trialists' Collaboration (2002)[42] | Peripheral angioplasty subgroup | 946 | Antiplatelet therapy vs placebo | Vascular death, myocardial infarction, or stroke | Bleeding | Efficacy: odds reduction 29% (standard error, 35%) |
| Aspirin | | | | | | |
| Cochrane systematic review (2012)[57] | Percutaneous transluminal angioplasty | 356 | Aspirin plus dipyridamole vs placebo | Restenosis or reocclusion | Bleeding | Efficacy: OR, 0.69 (95% CI, 0.44–1.10) |
| Clopidogrel | | | | | | |
| CAMPER† | Infrainguinal endovascular intervention | N/A | Clopidogrel plus aspirin vs aspirin alone | N/A | N/A | Trial stopped early because of poor enrollment |
| MIRROR (2013)[58] | Femoropopliteal endovascular intervention | 80 | Clopidogrel plus aspirin vs aspirin alone | Target lesion revascularization | Bleeding not reported | Efficacy: 5% vs 20%, $P$=0.04 |
| Cilostazol | | | | | | |
| Iida (2008)[59] | Femoropopliteal endovascular intervention | 127 | Cilostazol plus aspirin vs ticlopidine plus aspirin | Vascular patency | Bleeding not reported | Efficacy: OR, 0.32 (95% CI, 0.13–0.76) |
| Soga (2009)[60] | Femoropopliteal endovascular intervention | 78 | Cilostazol plus ASA vs. ASA alone | Adjudicated target vessel revascularization | Bleeding | Efficacy: 84.6% vs. 62.2%, $P$=0.04<br>Safety: No major bleeding events in either group |
| STOP-IC (2013)[61] | Femoropopliteal endovascular intervention | 200 | Cilostazol plus ASA vs. ASA alone | Adjudicated angiographic restenosis | Bleeding not reported | Efficacy: OR 0.26 (95% CI, 0.13-0.53) |
| Anticoagulation | | | | | | |
| ePAD (2015)‡ | Femoropopliteal endovascular intervention | 203 | Edoxaban vs clopidogrel plus aspirin | Adjudicated restenosis or reocclusion | Adjudicated TIMI and ISTH bleeding | Efficacy: RR, 0.89 (95% CI, 0.59–1.34)<br>Safety: RR, 0.20, (95% CI, 0.02–1.70) (ISTH) |

CAMPER indicates Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization; CI, confidence interval; ePAD, Edoxaban in Patients with Peripheral Artery Disease; ISTH, International Society on Thrombosis and Haemostasis; MIRROR, Follow-up Management of Peripheral Arterial Intervention with Clopidogrel; N/A, not applicable; OR, odds ratio; RR, relative risk; and TIMI, Thrombolysis in Myocardial Infarction.

*Bleeding assessed by a variety of measures, including ascertainment of adverse events and/or various bleeding scores without clearly defined adjudication parameters.

†William R. Hiatt, MD, personal communication, 2016.

‡Frans L. Moll, MD, PhD, unpublished data, 2015.

the primary safety end point was adjudicated Thrombolysis in Myocardial Infarction and International Society on Thrombosis and Haemostasis bleeding. At 6 months after procedure, there were numerically fewer restenosis or reocclusion events with edoxaban compared with clopidogrel (RR, 0.89; 95% CI, 0.59–1.34). There were no Thrombolysis in Myocardial Infarction major or life-threatening bleeding events in the edoxaban group, whereas there were 2 major and 2 life-threatening bleeding events in the clopidogrel group. By International Society on Thrombosis and Haemostasis criteria, there was 1 major and 1 life-threatening bleeding event versus 5 major and 2 life-threatening bleeding events in the edoxaban and clopidogrel arms, respectively (RR, 0.20; 95% CI, 0.02–1.70). These preliminary data suggest

that edoxaban versus clopidogrel in addition to aspirin in patients with PAD undergoing femoropopliteal endovascular treatment may improve vascular patency and reduce the risk for major and life-threatening bleeding events.

## Antithrombotic Therapy After Surgical Peripheral Revascularization

As with endovascular procedures, the goal of antithrombotic treatment after surgical revascularization is to improve procedural success and mitigate MACE while limiting antithrombotic-related bleeding risk. However, surgical revascularization can induce a prothrombotic state with disturbances of the coagulation and fibrinolytic systems,[92,93] imposing an increased risk for occlusion of the vascular reconstruction. Consequently, a different antithrombotic treatment strategy after surgical compared with endovascular revascularization may be required to improve outcomes after surgery. To date, few randomized studies have addressed this issue, and some suffer from major limitations (Table 3).

### *Aspirin*

Aspirin plus dipyridamole was no better than placebo at maintaining patency in 549 patients after femoropopliteal saphenous vein bypass.[62] In a large meta-analysis performed by the Antithrombotic Trialists' Collaboration and published in 1994,[56] 11 randomized studies on antiplatelet treatment versus placebo after lower limb bypass surgery (n=2437) were included. In this prespecified subgroup analysis, any antiplatelet therapy (mainly aspirin) was associated with a 38% (standard deviation 9%, *P*=0.00001) relative risk reduction for graft occlusion, regardless of whether low- or high-dose aspirin was used. Any antiplatelet therapy was also associated with a 22% odds reduction in vascular death, MI, or stroke among patients undergoing peripheral grafting.[42]

A more recent Cochrane systematic review, including 16 randomized studies (total n=5638) on different postoperative antiplatelet treatment strategies after lower limb bypass procedures, concluded that aspirin (with or without dipyridamole) versus placebo or no treatment was associated with improved primary patency of the vascular reconstruction at 1 year (OR, 0.42; 95% CI, 0.22–0.83).[63] In a further subgroup analysis, this benefit was mainly driven by an effect on prosthetic bypass procedures (OR, 0.19; 95% CI, 0.10–0.36). Thus, according to currently available evidence, aspirin improves patency after lower limb revascularization procedures, particularly those using prosthetic conduits. However, the efficacy of aspirin alone has been questioned, especially after autologous vein bypass,[94,95] and individual patient factors, such as continued cigarette smoking, may negatively affect the efficacy of aspirin treatment after surgical revascularization.[96]

### *Ticlopidine*

Ticlopidine versus placebo was demonstrated to markedly improve saphenous vein graft patency at 2 years (66.4% versus 51.2%, *P*=0.02).[88] Ticlopidine also reduced reocclusion after femoropopliteal thromboendarterectomy compared with placebo (12% versus 52%, *P*=0.003).[65] Because of unusual but potentially serious side effects of neutropenia and bone marrow aplasia, ticlopidine is not widely used.

### *Clopidogrel*

Clopidogrel has not yet been studied versus placebo or monotherapy with aspirin after lower limb surgical revascularization. However, 851 patients undergoing below-knee femoropopliteal bypass were randomized to clopidogrel plus aspirin versus aspirin alone in the CASPAR trial (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Artery Disease).[66] The primary efficacy end point was a composite of graft occlusion, ipsilateral revascularization, above-ankle amputation of affected limb, or death at 24 months, whereas severe bleeding was the primary safety end point. Among all studied patients, the primary efficacy end point was similar between groups. In the subgroup receiving prosthetic conduits (n=253), the addition of clopidogrel was associated with reduced risk of the primary efficacy end point (HR, 0.65; 95% CI, 0.45–0.95; *P*=0.03). This result should be interpreted with caution because the patients were not stratified for type of surgical conduit at randomization. Furthermore, the use of DAPT increased severe and moderate bleeding compared with aspirin alone (HR, 2.84; 95% CI, 1.32–6.08). In contrast to these overall negative results, a pilot study of clopidogrel plus aspirin compared with aspirin alone showed improved surrogate biomarkers of atherothrombosis and cardiac injury in patients undergoing surgery for CLI, demonstrating a theoretical benefit of DAPT after surgery in terms of cardiovascular outcomes.[67]

### *Anticoagulation*

Data supporting the use of anticoagulation after surgical revascularization for PAD are mixed. Among 116 patients undergoing femoropopliteal or more distal bypass surgery randomized to dicoumarol or no anticoagulation, 3-year primary graft patency was similar between treatment arms (46% versus 42%, *P*=0.88) and serious bleeding complications occurred in 4% to 5% of patients taking coumarin.[68] The largest study of anticoagulation after surgical peripheral revascularization was the Dutch BOA trial (Dutch Bypass Oral Anticoagulants or Aspirin) (n=2690) comparing vitamin K antagonists to aspirin after infrainguinal bypass grafting.[69] The primary end point was adjudicated graft occlusion, and mean follow-up was 21 (range 0–45) months. In the main analysis population, vitamin K antagonists did not confer any benefit over aspirin (HR,




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**Table 3. Antithrombotic Therapy After Surgical Revascularization for Peripheral Arterial Disease**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Primary Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| Meta-analyses of various antiplatelet agents | | | | | | |
| Antithrombotic Trialists' Collaboration (1994)[56] | Peripheral graft subgroup | 2437 | Antiplatelet therapy vs placebo | Vascular occlusion | Bleeding* | Efficacy: odds reduction 38% (standard deviation, 9%) |
| Antithrombotic Trialists' Collaboration (2002)[42] | Peripheral graft subgroup | 2497 | Antiplatelet therapy vs placebo | Vascular death, myocardial infarction, or stroke | Bleeding | Efficacy: odds reduction 22% (standard error, 16%) |
| Aspirin | | | | | | |
| McCollum (1991)[62] | Femoropopliteal saphenous vein bypass | 549 | Aspirin plus dipyridamole vs placebo | Graft patency | Bleeding | Efficacy: 61% vs 60%, *P*=0.43 |
| Cochrane systematic review (2015)[63] | Infrainguinal bypass | 954 | Aspirin or aspirin plus dipyridamole vs placebo | Primary graft patency | Bleeding | Efficacy: OR, 0.42 (95% CI, 0.22–0.83)<br>Safety: OR, 1.88 (95% CI, 0.85–4.16) |
| Ticlopidine | | | | | | |
| Becquemin (1997)[64] | Femoropopliteal or femorotibial saphenous vein bypass graft | 243 | Ticlopidine vs placebo | Adjudicated graft patency | Adjudicated bleeding† | Efficacy: 66.4% vs 51.2%, *P*=0.02 |
| Castelli (1986)[65] | Femoropopliteal thrombendarterectomy | 50 | Ticlopidine vs placebo | Reocclusion | | Efficacy: 12% vs 52%, *P*=0.003 |
| Clopidogrel | | | | | | |
| CASPAR (2010)[66] | Below-knee bypass graft | 851 | Clopidogrel plus aspirin vs aspirin | Adjudicated index graft occlusion or revascularization, above-ankle amputation, or death | Adjudicated GUSTO severe bleeding | Efficacy: HR, 0.98 (95% CI, 0.78–1.23)<br>Safety: 2.1% vs 1.2%, *P*=NS |
| Burdess (2010)[67] | Infrainguinal bypass, femoral endarterectomy, or lower limb amputation for critical limb ischemia | 108 | Clopidogrel plus aspirin vs aspirin alone | Adjudicated positive cardiac troponin | Major bleeding according to CURE criteria | Efficacy:<br>RR, 0.93 (95% CI, 0.39–2.17)<br>Safety: RR, 1.4 (95% CI, 0.49–3.76) |
| Anticoagulation | | | | | | |
| Arfvidsson (1989)[68] | Femoropopliteal or femorodistal bypass surgery | 116 | Dicumarol vs control | Primary graft patency | Bleeding | Efficacy: 46% vs 42%, *P*=0.88 |
| Dutch BOA (2000)[69] | Infrainguinal bypass graft | 2690 | Phenprocoumon or acenocoumarol vs aspirin | Adjudicated graft occlusion | Adjudicated major bleeding† | Efficacy: HR, 0.95 (95% CI, 0.82–1.11)<br>Safety: HR, 1.96 (95% CI, 1.42–2.71) |
| Anticoagulation plus antiplatelet therapy | | | | | | |
| Sarac (1998)[70] | Infrainguinal bypass grafting with autogenous vein and high risk for graft failure | 56 | Warfarin plus aspirin vs aspirin | Primary graft patency | Bleeding | Efficacy: 74% vs 51%, *P*=0.04 |

(*Continued*)

**Table 3. Continued**

| Variable | Study Population | Number of Subjects | Treatment | Primary Efficacy End Point(s) | Primary Safety End Point(s) | Result |
|---|---|---|---|---|---|---|
| Johnson (2002)[71] | Axillofemoral, femorofemoral, femoropopliteal, or femorodistal bypass surgery | 831 | Warfarin plus aspirin vs aspirin | Graft patency | Bleeding | Efficacy: Prosthetic graft RR, 0.62 (95% CI, 0.42–1.92) Vein bypass RR, 1.04 (95% CI, 0.72–1.51) Safety: 8.4% vs 3.6%, *P*=0.02 |
| Monaco (2012)[72] | Femoropopliteal bypass surgery | 341 | Warfarin (international normalized ratio, 2.0–2.5) plus clopidogrel vs aspirin plus clopidogrel | Coprimary 1: Graft patency Coprimary 2: Freedom from severe peripheral ischemia leading to amputation | Bleeding | Efficacy: Coprimary 1: 86.7% vs 80.8%, *P*=0.03; Coprimary 2: 77.6% vs 63.9%, *P*=0.04 Safety: 4.63% vs 2.99%, *P*=0.06 |
| Jivegard (2005)[73] | Peripheral arterial bypass graft for critical limb ischemia | 284 | Dalteparin plus aspirin vs placebo plus aspirin | Primary graft patency | Bleeding | Efficacy: 59% vs 59%, *P*=NS |

CASPAR, Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease; CI, confidence interval; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; Dutch BOA, Dutch Bypass Oral Anticoagulants or Aspirin Study; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR, hazard ratio; NS, not significant; OR, odds ratio; and RR, relative risk.

*Bleeding assessed by a variety of measures, including ascertainment of adverse events and/or various bleeding scores without clearly defined adjudication parameters.

†Prospectively defined and collected bleeding events not assessed with a defined bleeding scale.



0.95; 95% CI, 0.82–1.11). In the subgroup receiving autologous vein grafts, vitamin K antagonism was associated with a reduction in graft occlusion (HR, 0.69; 95% CI, 0.54–0.88), whereas study treatment was associated with a greater risk of graft occlusion among patients receiving prosthetic grafts (HR, 1.26; 95% CI, 1.03–1.55). However, patients were not stratified for graft material at randomization. In addition, the target international normalized ratio for vitamin K antagonism in this trial was 3 to 4.5; although patients receiving study drug were within this treatment range only ≈50% of the time, adjudicated major bleeding complications were significantly higher with vitamin K antagonists than with aspirin (HR, 1.96; 95% CI, 1.42–2.71).

Although not tested in a randomized fashion, observations such as those in the Dutch BOA study suggest that bypass graft material may influence the effect of specific classes of antithrombotic agents. A recent Cochrane systematic review (14 studies, n=4970) exploring several different antithrombotic treatment strategies after infrainguinal bypass surgery concluded that patients receiving infrainguinal autologous vein bypass surgery are more likely to benefit from vitamin K antagonists than from platelet inhibitors.[97] Conversely, patients receiving prosthetic bypass surgery may derive more benefit from platelet inhibition. However, the evidence for vitamin K antagonist use after venous bypass was considered weak and partly inconsistent in the Cochrane report: 4 of the 14 included studies compared a vitamin K antagonist versus no anticoagulation (with 2 studies performed on a background of aspirin), whereas 2 other studies used aspirin or aspirin plus dipyridamole as the comparator.[97]

### *Anticoagulation Plus Antiplatelet Therapy*

Several studies have examined the effect of anticoagulation plus antiplatelet therapy after surgical revascularization for PAD. Warfarin plus aspirin versus aspirin alone was studied in 56 patients undergoing infrainguinal bypass grafting with autogenous vein.[70] Combination therapy improved primary graft patency at 3 years (74% versus 51%, *P*=0.04), but postoperative hematoma complications were more frequent (32% versus 3.7%, *P*=0.004). Among 831 patients undergoing peripheral arterial bypass surgery randomized to warfarin plus aspirin versus aspirin alone and stratified by graft material, primary patency rates were similar among patients with prosthetic bypasses (RR, 0.62; 95% CI, 0.42–1.92) and vein bypasses (RR, 1.04; 95% CI, 0.72–1.15).[71] There was a suggestion of benefit for warfarin plus aspirin among subgroups of patients with 6-mm versus 8-mm prosthetic bypass grafts and those with prosthetic femoropopliteal grafts in the above-knee position. Major bleeding was greater among patients assigned to combination therapy

(8.4% versus 3.6%, *P*=0.02). In an open-label, pseudo-randomized study,[72] low-intensity (international normalized ratio, 2.0–2.5) warfarin plus clopidogrel versus aspirin plus clopidogrel was tested in 341 patients undergoing femoropopliteal artery bypass grafting for IC or CLI. Graft patency and amputation for severe peripheral ischemia were coprimary end points, although the study sample size determination was based on the former end point, and events were not adjudicated. In this study, treatment with warfarin plus clopidogrel versus aspirin plus clopidogrel was associated with improved graft patency (*P*=0.03) and less amputation (*P*=0.04) during long-term follow-up. Minor but not major bleeding episodes were more common among patients treated with warfarin plus clopidogrel, although the study was not powered to detect hemorrhagic complications.

Beyond reducing thrombotic complications that may threaten graft patency, anticoagulation with unfractionated or low-molecular-weight heparin, which experimentally inhibits smooth muscle cell proliferation, may also improve longer term graft patency by reducing neointimal hyperplasia.[73] In this context, Jivegård et al tested the efficacy of adjuvant treatment with dalteparin, a low-molecular-weight heparin, versus placebo for 3 months after aortoiliac or infrainguinal bypass grafting in patients with CLI.[73] Among 284 patients, adjuvant treatment with dalteparin did not confer any patency benefit at either 3 months or 1 year after the vascular procedure.

## Guideline Recommendations for Antithrombotic Therapy After Peripheral Arterial Revascularization

Current guideline recommendations for antithrombotic therapies after revascularization for PAD are variable and do not always conform to the level of evidence available. Class I recommendations from the European Society of Cardiology advise treatment with aspirin in all patients undergoing angioplasty to reduce systemic vascular events, despite the absence of any data supporting this claim, at least 1 month of aspirin plus a thienopyridine after infrainguinal bare-metal stent implantation, also without any direct evidence, and aspirin or aspirin plus dipyridamole after infrainguinal bypass surgery.[15] Class IIb recommendations include use of vitamin K antagonists after autogenous vein infrainguinal bypass surgery and aspirin plus clopidogrel for patients with below-knee prosthetic graft bypass. These recommendations are based on data from overall negative trials with potential benefit in subgroup analyses. As discussed, these data can inform the design of future trials but should not be used to make treatment decisions. In contrast, the American College of Chest Physicians recommends single antiplatelet therapy with aspirin or clopidogrel in all patients after angioplasty with or without stenting (grade 1A) and after surgical revascularization (grade 1A), except for patients receiving prosthetic conduits in the below-knee position, for whom aspirin plus clopidogrel is suggested for 1 year after revascularization (grade 2C but without conclusive evidence).[16] The Society for Vascular Surgery practice guidelines recommend aspirin, clopidogrel, or aspirin plus clopidogrel in patients undergoing lower extremity bypass (venous or prosthetic, grade 2B) and at least 30 days of aspirin plus clopidogrel in patients undergoing infrainguinal endovascular intervention (grade 2B).[17] However, as noted earlier, the CASPAR trial assessing DAPT in lower extremity bypass was an overall negative trial. In the recently updated guideline from the American College of Cardiology and the American Heart Association, a grade IIb (level of evidence C) recommendation for DAPT with aspirin and clopidogrel to reduce the risk of limb-related events after lower extremity revascularization exists, which again suffers from the limitations described earlier.[5] Although not entirely updated to include recent data, the second TASC Consensus Document recommends single antiplatelet therapy, started before the procedure and continued indefinitely, as a first-line treatment after lower limb endovascular or surgical revascularization (grade A).[6] These important discrepancies in guideline recommendations for antithrombotic treatment after lower extremity revascularization reflect the paucity of high-quality data in this area and may contribute to the variation in the use of antithrombotic therapies observed in practice after procedure.

Despite a lack of evidence to support its use, many operators currently treat patients with a variable course of DAPT with aspirin and clopidogrel after peripheral revascularization. Data from the Swedish National Registry for Vascular Surgery demonstrate baseline treatment with aspirin monotherapy before revascularization and the addition of clopidogrel postprocedure, typically for 3 months, for 19% and 13% of CLI and IC patients, respectively.[12] In the United States, a study of 85 830 patients undergoing peripheral vascular intervention revealed that after procedure, 18.3% were treated with an oral anticoagulant, 19.1% received no P2Y12 inhibitor, 30.8% received a P2Y12 inhibitor before and after the procedure, 6.2% were treated with a P2Y12 inhibitor for ≤30 days, and 25.6% received a P2Y12 inhibitor for >30 days.[98] In this study, P2Y12 inhibitor use differed according to physician specialty and the clinical setting of the procedure. In a survey of members of the Peripheral Vascular Surgery Society, aspirin plus clopidogrel was the most commonly prescribed regimen after lower extremity endovascular intervention, with distal lesion location and stent placement associated with greater use of this combination.[99] Although there was no consensus regarding the optimal duration of treatment with aspirin plus

clopidogrel, a 1- to 3-month course was the most common. Furthermore, many peripheral intervention device trials recommend treatment with aspirin for ≥6 months or indefinitely plus clopidogrel for 1 to 3 months.[90] As demonstrated, current regimens for antithrombotic therapy after procedure are varied and unsupported by clinical trial data.

## Summary and Future Directions

Antithrombotic therapies play a critical role in the management of the patient with stable PAD and an even more important role in patients undergoing peripheral revascularization. This review has highlighted the limitations of current clinical trial data, including the central role of aspirin in maintaining the patency of the procedure and possibly reducing cardiovascular events after surgery, which is based on older data that do not reflect contemporary background therapy. More potent antiplatelet therapies and combinations of those therapies also have limited evidence for use after revascularization. For example, the use of DAPT is quite common, with even more prolonged use being promoted without any clear benefit after peripheral revascularization. Currently available clinical trial data for antithrombotic therapy after peripheral revascularization have been discussed in this review and are summarized according to the quality of study components in Figures 4 and 5.[11,37–41,43,44,48,51,53,55,58–62,64–73] What are clearly lacking and needed are adequately powered trials of antithrombotic therapy after peripheral revascularization in a primary PAD population with adjudicated MACE, MALE, and bleeding end points (Figure 3).

A review of clinicaltrials.gov shows few studies that will meet this need. The ASPIRE trial (Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities) (URL: http://clinicaltrials.gov. Unique identifier: NCT02217501) is an ongoing study of the effect of clopidogrel on a background of low-dose aspirin for a clinically indicated duration versus an additional 12 months on rates of primary patency, limb salvage, MI, ischemic stroke, or survival among patients undergoing endovascular treatment for PAD. The LONGDAPTPAD study (Effects of Prolonged DAPT after Lower Extremity Percutaneous Transluminal Angioplasty in Patients with LE-PAD) (URL: http://clinicaltrials.gov. Unique identifier: NCT02798913) is currently randomizing patients with PAD treated with endovascular peripheral revascularization to 3 months versus 12 months of clopidogrel plus aspirin; MACE and MALE are the primary outcomes for this study. Another randomized trial (URL: http://clinicaltrials.gov. Unique identifier: NCT02433587) plans to examine the effect of 1 versus 6 months of clopidogrel plus aspirin after endovascular PAD revascularization on MACE and MALE outcomes. Although these studies involve primary PAD populations and examine systemic and limb-related outcomes, each study is small (<500 patients), and full details regarding end point definitions and adjudication are not yet available. Lastly, the VOYAGER PAD trial (Vascular Outcomes Study of Aspirin along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) (URL: http://clinicaltrials.gov. Unique identifier: NCT02504216) is evaluating the addition of low-dose rivaroxaban to a background of aspirin after lower extremity revascularization. Estimated enrollment is 6500 patients, and the primary outcome is time to first MI, ischemic stroke, cardiovascular death, ALI, or major amputation for a vascular etiology.

Despite the additional insight into the field that these trials may provide, results are several years out, and additional trials will be necessary to develop the optimal

| | Primary PAD population and adjudicated efficacy endpoint | Pre-specified PAD subgroup and adjudicated efficacy endpoint | Post-hoc PAD subgroup or non-adjudicated efficacy endpoint |
|---|---|---|---|
| Adjudicated bleeding using standardized scale | EUCLID[38]<br>WAVE[53] | CHARISMA[39]<br>TRACER[51]<br>TRA2P[11] | PLATO[48]<br>PEGASUS[41]<br>ROCKET-AF[55] |
| Adjudicated bleeding using trial-specific scale | AAA[37] | | |
| Non-adjudicated bleeding or bleeding not reported | CLIPS[43]<br>POPADAD[44] | CAPRIE[40] | Antithrombotic Trialists' Collaboration[42,56] |

**Figure 4. Classification of trials of antithrombotic therapy for stable PAD.**
Trials of antithrombotic therapy for stable PAD are classified according to criteria related to study population and efficacy and bleeding end points. PAD indicates peripheral artery disease.

| | Primary PAD population and adjudicated efficacy endpoint | Pre-specified PAD subgroup and adjudicated efficacy endpoint | Post-hoc PAD subgroup or non-adjudicated efficacy endpoint |
|---|---|---|---|
| Adjudicated bleeding using standardized scale | CASPAR[62]<br>ePAD* | | |
| Adjudicated bleeding using trial-specific scale | Becquemin et al[64]<br>Burdess et al[67]<br>Dutch BOA[69] | | |
| Non-adjudicated bleeding or bleeding not reported | MIRROR[58]<br>Monaco et al[72]<br>Soga[60]<br>STOP-IC[61] | | Antithrombotic Trialists' Collaboration[42,56]<br>Iida et al[59]<br>McCollum et al[62]<br>Castelli et al[65]<br>Arfvidsson et al[68]<br>Sarac et al[70]<br>Johnson et al[71]<br>Jivegard et al[73] |

**Figure 5. Classification of trials of antithrombotic therapy after peripheral revascularization.**
Trials of antithrombotic therapy after peripheral revascularization are classified according to criteria related to study population and efficacy and bleeding end points. *Frans L. Moll, MD, PhD, unpublished data, 2015. PAD indicates peripheral artery disease.

strategies to prevent both cardiac and limb events after revascularization while minimizing bleeding risk. Given the beneficial effects of vorapaxar on ALI seen in patients with symptomatic PAD,[13] the use of vorapaxar after peripheral revascularization may represent a rational pathway for future investigation. Highlighted in this review are the required key components of a rigorous clinical trial of antithrombotic therapy after peripheral revascularization. However, there is limited capacity to answer all scientific inquiries with large-scale randomized clinical trials, necessitating the development of novel study designs. From a methodologic perspective, leveraging existing large registries or electronic medical records for randomized trials may provide an alternative approach to evaluate new therapeutics in the setting of PAD revascularization. Although challenges to using these strategies exist, they could potentially reduce costs and provide more generalizable results. Given the large burden of disease, the high risk of the population, and the current state of the field, tremendous opportunity exists for clinician-scientists to design high-quality studies that will help guide treatment of and optimize care for patients with PAD.

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## DISCLOSURES

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## FOOTNOTES

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