Antithrombotic Therapy in Peripheral Artery Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: This guideline focuses on antithrombotic drug therapies for primary and secondary prevention of cardiovascular disease as well as for the relief of lower-extremity symptoms and critical ischemia in persons with peripheral arterial disease (PAD).

Methods: The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.

Results: The most important of our 20 recommendations are as follows. In patients aged ≥ 50 years with asymptomatic PAD or asymptomatic carotid stenosis, we suggest aspirin (75-100 mg/d) over no therapy (Grade 2B) for the primary prevention of cardiovascular events. For secondary prevention of cardiovascular disease in patients with symptomatic PAD (including patients before and after peripheral arterial bypass surgery or percutaneous transluminal angioplasty), we recommend long-term aspirin (75-100 mg/d) or clopidogrel (75 mg/d) (Grade 1A). We recommend against the use of warfarin plus aspirin in patients with symptomatic PAD (Grade 1B). For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, we suggest single rather than dual antiplatelet therapy (Grade 2C). For patients with refractory claudication despite exercise therapy and smoking cessation, we suggest addition of cilostazol (100 mg bid) to aspirin (75-100 mg/d) or clopidogrel (75 mg/d) (Grade 2C). In patients with critical limb ischemia and rest pain unable to undergo revascularization, we suggest the use of prostanoids (Grade 2C). In patients with acute limb ischemia due to acute thrombosis or embolism, we recommend surgery over peripheral arterial thrombolysis (Grade 1B).

Conclusions: Recommendations continue to favor single antiplatelet therapy for primary and secondary prevention of cardiovascular events in most patients with asymptomatic PAD, symptomatic PAD, and asymptomatic carotid stenosis. Additional therapies for relief of limb symptoms should be considered only after exercise therapy, smoking cessation, and evaluation for peripheral artery revascularization.   *CHEST 2012; 141(2)(Suppl):e669S–e690S*

Abbreviations: ABI = ankle brachial index; CAD = coronary artery disease; CAPRIE = Clopidogrel vs Aspirin in Patients at risk for Ischemic Events; MI = myocardial infarction; MWD = maximum walking distance; PAD = peripheral arterial disease; PTA = percutaneous transluminal angioplasty; RCT = randomized controlled trial; RR = risk ratio; rt-PA = recombinant tissue-type plasminogen activator

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1. For persons with asymptomatic peripheral arterial disease (PAD), we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who

value preventing an MI substantially higher than avoiding a GI bleed, if they are in the moderate or high cardiovascular risk group, will be more likely to choose aspirin.

3.1-3.4. For secondary prevention patients with symptomatic PAD, we recommend one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A). **We suggest *not to use* dual antiplatelet therapy with aspirin plus clopidogrel** (Grade 2B). **We recommend *not to use* an antiplatelet agent with moderate-intensity warfarin** (Grade 1B).

4.1-4.4. For patients with intermittent claudication refractory to exercise therapy (and smoking cessation), we suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C); **we suggest against the use of pentoxifylline, heparinoids, or prostanoids** (Grade 2C).

5.1. For patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention, we suggest the use of prostanoids in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C).

Values and preferences: Patients who do not value uncertain relief of rest pain and ulcer healing greater than avoidance of a high likelihood of drug-related side effects will be disinclined to take prostanoids.

6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C); **we suggest reperfusion therapy (surgery or intraarterial thrombolysis) over no reperfusion therapy** (Grade 2C); **we recommend surgery over intraarterial thrombolysis** (Grade 1B). **In patients undergoing intraarterial thrombolysis, we suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase** (Grade 2C).

7.1. For patients undergoing peripheral artery percutaneous transluminal angioplasty (PTA) with or without stenting, we recommend long-term aspirin (75-100 mg/day) or clopidogrel (75 mg/day) (Grade 1A). **For patients undergoing peripheral artery PTA with stenting, we suggest**

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single rather than dual antiplatelet therapy (Grade 2C).

Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a definite increased risk of bleeding are more likely to choose to use dual antiplatelet therapy.

8.1-8.4. We recommend one of the following antithrombotic regimens to be continued long-term following peripheral artery bypass graft surgery over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A). **We recommend single antiplatelet therapy over antiplatelet therapy and warfarin** (Grade 1B). **In patients undergoing below-knee bypass graft surgery with prosthetic grafts, we suggest clopidogrel 75 mg/d plus aspirin (75-100 mg/d) over aspirin alone for 1 year** (Grade 2C). **For all other patients, we suggest single over dual antiplatelet therapy** (Grade 2B).

9.1. For persons with asymptomatic carotid stenosis, we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis.

9.2-9.3. In patients with symptomatic carotid stenosis (including recent carotid endarterectomy), we recommend long-term antiplatelet therapy with clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) or aspirin (75-100 mg once daily) over no antiplatelet therapy (Grade 1A). **We suggest either clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) over aspirin (75-100 mg)** (Grade 2B).

This article focuses on the use of antithrombotic drugs in patients with peripheral arterial disease (PAD). PAD is associated with a high prevalence of atherosclerosis in other vascular beds. The leading causes of morbidity and mortality in patients with PAD are myocardial infarction (MI) and stroke; therefore, as in patients with coronary artery disease (CAD), the primary benefit of antithrombotic therapy in this patient population is prevention of vascular events and mortality. The patient-important outcomes (ie, total mortality, nonfatal MI, nonfatal stroke, major nonfatal extracranial bleed) are the same outcomes considered for recommendations for CAD and stroke. However, we review the effects of antithrombotic therapy on outcomes specific to PAD (eg, rest pain of the limbs, quality of life, or amputation).

Studies evaluating antithrombotic therapy immediately following peripheral bypass graft surgery or percutaneous endovascular procedures generally have used graft patency or reocclusion as the primary end point. These outcomes are surrogates for patient-important outcomes of quality of life and limb amputation, which are seldom reported.

We consider the desirable and undesirable consequences of antithrombotic therapy in the following populations or patient groups: (1) persons with asymptomatic PAD, (2) patients with symptomatic PAD (including those with claudication or critical [chronic] limb ischemia and rest pain or prior peripheral arterial revascularization), (3) patients with acute limb ischemia and threatened limb loss, (4) patients following peripheral arterial revascularization, and (5) persons with asymptomatic and symptomatic carotid stenosis. Table 1 and Table S1 describe both the question definition (ie, population, intervention, comparator, and outcome) and the study types considered for each question. (Tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement. See the "Acknowledgments" for more information.)

High-quality evidence supports an effect of aspirin on vascular mortality. In addition, a recent meta-analysis provided moderate-quality evidence that long-term use of aspirin reduces mortality from specific cancer types.[1] In a population of patients with symptomatic vascular disease, vascular disease and cancer are the leading causes of death. Therefore, we have chosen total mortality over a 10-year period as the main outcome of interest. When data are available, we included fatal intracranial or extracranial bleeding with vascular death or total mortality under the general category of antithrombotic therapy-related deaths. Nonfatal hemorrhagic strokes and ischemic strokes are included together as nonfatal strokes. Although the former is a complication and decrease in the latter is a beneficial effect of antithrombotic therapy, their impact on patient morbidity is similar.

1.0 Methods

Estimation of Baseline Risks and Absolute Effects of Treatment

In order to estimate absolute benefits and harms associated with a given therapy, we performed the following steps. First,

Table 1—[Introduction] Structured Clinical Questions

Section	Informal Question	Population	Intervention	Comparator	Outcome
			PICO Question		
2.0 Asymptomatic PAD					
2.1	Choice of antithrombotic therapy	Patients with asymptomatic PAD (eg, ABPI < 0.9)	Aspirin	Placebo	Total mortality; Nonfatal MI; Nonfatal stroke; Major nonfatal extracranial bleeding
3.0 Symptomatic PAD: prevention of cardiovascular events					
3.1	Choice of antithrombotic therapy	Patients with symptomatic PAD	Aspirin	Placebo	Total mortality; Nonfatal MI; Nonfatal stroke; Major nonfatal extracranial bleeding
3.2			Clopidogrel	Aspirin	
3.3			Aspirin + clopidogrel	Aspirin	
3.4			Aspirin + oral anticoagulants	Aspirin	
4.0 Symptomatic PAD: management of claudication					
4.1	Choice of antithrombotic therapy	Patients with claudication	Heparins	Placebo	Quality of life; Maximum walking distance; Major nonfatal extracranial bleeding; Mortality; Adverse events
4.2			Cilostazol	Placebo or pentoxifylline	
4.3			Pentoxifylline	Placebo	
4.4			Prostaglandins	Placebo	
5.0 Symptomatic PAD: management of critical limb ischemia					
5.1	Choice of antithrombotic therapy	Patients with critical limb ischemia unable to undergo revascularization	Prostaglandins	Placebo	Rest-pain relief; Ulcer healing; Amputations; Mortality; Adverse events
6.0 Acute limb ischemia					
6.1	Choice of antithrombotic therapy	Patients with acute limb ischemia	Unfractionated heparin	No anticoagulation	Death; Amputation; Nonfatal stroke
6.2			Intraarterial thrombolytic therapy	Surgery	
6.3			Urokinase or rt-PA	Streptokinase	Major nonfatal extracranial bleeding
7.0 Endovascular surgery					
7.1	Choice of antithrombotic therapy post-PTA ± stent	Patients undergoing PTA	Aspirin plus dipyridamole	Placebo	Vessel restenosis/occlusion
			Aspirin/dipyridamole	Phenprocoumon	
			Ticlopidine	Phenprocoumon	
			Unfractionated heparin	Subcutaneous nadroparin (LMWH)	

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO Question		
		Population	Intervention	Comparator	Outcome
		8.0 Open lower-limb vascular surgery			
8.1	Choice of antithrombotic therapy	Patients undergoing any graft	Aspirin or aspirin/dipyridamole	Placebo	Vascular mortality
8.2			Aspirin or aspirin/dipyridamole	Other agents	Nonfatal MI
8.3			Clopidogrel plus aspirin	Aspirin	Nonfatal stroke
8.4			Oral anticoagulants ± aspirin	Aspirin	Major nonfatal extracranial bleeding
8.5		Patients undergoing below-knee prosthetic graft	Aspirin plus clopidogrel	Aspirin	Amputation
		9.0 Carotid stenosis			
9.1	Choice of antithrombotic therapy	Patients with asymptomatic carotid stenosis	Aspirin	Placebo	Total mortality
					Nonfatal MI
					Nonfatal stroke
			Antiplatelet agents post endarterectomy	Placebo	Major nonfatal extracranial bleeding
9.2		Patients with symptomatic carotid stenosis			
9.3		Patients with carotid stenosis undergoing endarterectomy			

ABPI = ankle-brachial pressure index; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PAD = peripheral arterial disease; PICO = population, intervention, comparator, outcome; PTA = percutaneous transluminal angioplasty; rt-PA = recombinant tissue-type plasminogen activator.

we generated relative effect estimates (relative risks) from the highest-quality published meta-analysis of randomized controlled trials (RCTs). If no such meta-analyses were available or were out of date, we conducted our own meta-analyses of relevant RCTs or used relative risk estimates from single RCTs in the absence of other relevant RCTs.

Ideally, in order to approximate the benefit of a given therapy in the real world, estimates of baseline risk (control group risks) would be derived from population-based observational studies. Unfortunately, for most of our clinical questions, we were unable to identify observational studies of sufficient quality that reported all relevant outcomes. In such cases, we derived control group risk estimates from a representative control arm of a relevant meta-analysis or RCT and adjusted them to our specified time frame. Detailed explanations of our choices are presented in each section.

Values and Preferences

The relative weight given to outcomes (eg, an extracranial bleed compared with an MI or a stroke) greatly affects the trade-offs between desirable and undesirable consequences of antithrombotic therapy. Unfortunately, limited data guide us with respect to the relative impact of these events on a patient's quality of life.[2] As described in Guyatt et al,[3] in this supplement we have used ratings from participating guideline panelists' estimates of patient valuation of the outcomes of interest. The ratings suggest that nonfatal major extracranial bleeding (which is usually readily treated and with few long-lasting consequences) carries only slightly less weight than a nonfatal MI (which also often has limited long-term consequences) but substantially less weight than a stroke (which often is associated with long-term disability). Our decisions are based on a disutility or negative weight of stroke of three times the disutility of a major extracranial bleed.

Trade-offs between desirable and undesirable consequences of alternative management strategies sometimes represent close-call situations. In making recommendations in such situations, we have taken a *primum non nocere* (first do no harm) approach, placing the burden of proof with those who would claim a benefit of treatment. In other words, when a treatment is associated with uncertain benefit and an appreciable probability of important harm, we recommend against such treatment.

We identified the relevant evidence for our clinical questions with the assistance of a team of methodologists and medical librarians as outlined in Guyatt et al.[3] Systematic literature searches for systematic reviews and original studies were performed until the date of January 15, 2010. After that date, we scanned the literature regularly, although this was not performed as systematic literature searches.

2.0 PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH ASYMPTOMATIC PAD

As in the article by Vandvik et al[4] of this supplement, primary prevention refers to the use of an intervention to prevent events prior to any clinically manifested disease. Hence, even though nearly every 70-year-old man or woman has significant vascular changes, they are candidates for primary (as opposed to secondary) prevention unless they have clinically manifested vascular disease (ie, claudication; history of peripheral vascular procedures; known history of CAD, MI, or stroke).

Most asymptomatic patients with PAD will be identified through ankle-brachial index (ABI) screening. The ABI is the ratio of the highest systolic BP in the lower limb to that of the arm. This relatively simple clinical test was originally used to confirm the diagnosis of PAD and assess its severity. Low ABI (<0.90) has been shown to be an independent predictor of MI, stroke, and vascular mortality independent of other cardiovascular risk factors.[5-9] The ABI, therefore, has been promoted as a simple, inexpensive, noninvasive screening tool for the assessment of future cardiovascular risk. In a meta-analysis of ∼48,000 healthy men and women, ABI <0.90 at baseline was associated with an approximate doubling of the 10-year mortality, cardiovascular mortality, and major coronary event rate after adjusting for the Framingham risk score.[10]

Therefore, when evaluating a patient for primary prevention with aspirin, we suggest using a risk stratification tool such as the Framingham risk score, which provides estimates of low ($<10\%$), moderate (10%-20%), and high risk ($>20\%$) of cardiovascular events over 10 years. If, in addition, the patient has an ABI <0.90, we suggest doubling this score, thus possibly increasing the patient's risk from a low to moderate or a moderate to high category.[10]

2.1 Aspirin

We consider the evidence for aspirin therapy for the primary prevention of CAD (see section 1.1 in Vandvik et al[4] in this supplement) applicable to patients with asymptomatic PAD. On the basis of an individual participant data meta-analysis,[11] aspirin would be expected to prevent 19 and 31 nonfatal MIs and lead to 16 and 22 major extracranial bleeding events per 1,000 moderate- and high-risk patients treated, respectively (Table S2). In addition, long-term aspirin use has been associated with a significant decrease in cancer mortality,[12] likely contributing to the decrease in total mortality associated with long-term aspirin therapy observed in another meta-analysis.[13] On the basis of these data and regardless of vascular risk, aspirin use in 60-year-old men would also result in six fewer deaths (12 fewer to 0 fewer) per 1,000 patients treated for 10 years. The overall quality of evidence is moderate given the imprecision in the estimates for total mortality.

The relative effect of aspirin on prevention of vascular events, bleeding, and total mortality are likely similar in patients with cardiovascular risk factors, asymptomatic PAD, and asymptomatic carotid stenosis. Our recommendations for primary prevention in asymptomatic patients with PAD are therefore identical to those described in Vandvik et al.[4]

Recommendation

2.1. For persons with asymptomatic PAD, we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Antithrombotic Therapy in Peripheral Artery Disease

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced with an increase in major bleeding events. Whatever the risk status, people averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed, if they are in the moderate or high cardiovascular risk strata, will be more likely to choose aspirin.

3.0 SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH SYMPTOMATIC PAD

3.1-3.3 Antiplatelet Therapies for Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD

Because antiplatelet therapy would be expected to result in similar relative reductions in vascular events such as MI or stroke in patients with PAD or CAD, we considered RCTs enrolling patients with PAD, CAD, or both to support our recommendations for both conditions. Although many of the included studies conducted post hoc analyses limited to patients enrolled for symptomatic PAD, we did not find these subgroup analyses credible based on criteria proposed by Sun et al.[14] Therefore, our recommendations for antiplatelet therapy as secondary prevention of cardiovascular events in symptomatic patients with PAD are identical to those described in sections 2.1.1, 2.1.2, 2.1.3, and 2.1.5 of Vandvik et al.[4] For the reader's interest, we briefly review the pertinent evidence in the following sections.

3.1 Aspirin

Table S3 summarizes the quality of evidence and main findings from a meta-analysis of individual participant data from 16 randomized trials with 17,000 patients with established vascular disease (six trials of patients with previous MI and 10 of patients with previous transient ischemic attack or stroke).[11] In this population at high risk for a serious vascular event (8.2% yearly risk), aspirin significantly reduced total mortality, nonfatal MI, and nonfatal stroke but increased nonfatal extracranial bleeding events. The number of vascular events and total deaths prevented was far greater than the number of bleeding events that resulted from aspirin.

3.2 Clopidogrel vs Aspirin

The Clopidogrel vs Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial is the only randomized trial that directly compared clopidogrel and aspirin in secondary prevention of cardiovascular events, and we consider this trial to be the most credible source of evidence.[15] More than 19,000 patients with atherosclerotic vascular disease manifested as a recent stroke, recent MI, or symptomatic PAD received clopidogrel or aspirin. After a mean follow-up of 1.9 years, clopidogrel was associated with a possible reduction in nonfatal MI and nonfatal extracranial bleeding and little or no effect on total mortality. Table S4 summarizes the quality of evidence and main findings of the CAPRIE trial. The results indicate no effect of clopidogrel on total mortality compared with aspirin. These results are consistent with a meta-analysis of 10 studies examining the effects of thienopyridine derivatives (eg, clopidogrel, ticlopidine) vs aspirin in patients at high vascular risk.[16]

3.3 Dual Antiplatelet Therapy With Clopidogrel and Aspirin vs Single Antiplatelet Therapy

A Cochrane systematic review evaluated short- and long-term dual antiplatelet therapy in patients with established CAD.[17] Only one large-scale RCT, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, has evaluated the long-term efficacy of clopidogrel and aspirin vs aspirin alone.[18] This trial followed 15,603 patients with established vascular disease or multiple risk factors for a mean period of 28 months. Table S5 summarizes the quality of evidence and findings from this trial. Results of the study failed to demonstrate or exclude an effect of dual antiplatelet therapy relative to aspirin on total mortality or nonfatal MI. Dual antiplatelet therapy was associated with a possible reduction in nonfatal stroke and a possible increase in nonfatal extracranial bleeding. We considered the quality of evidence to be moderate because of imprecise effect estimates for all outcomes. Although this study included patients with other vascular diseases, we considered its findings directly applicable to patients with symptomatic PAD. We did not deem subgroup analyses suggesting different effects of dual antiplatelet therapy in symptomatic vs asymptomatic patients to be credible.[14]

3.4 Warfarin Plus Aspirin vs Aspirin Alone

Although studies comparing warfarin to placebo or aspirin have been conducted in patients with PAD, these have been small in size and focused on PAD-specific outcomes (eg, lower-extremity pain, bypass graft patency) rather than on rates of subsequent stroke, MI, or vascular death. Subsequent sections summarize these studies.

Of the available trials of patients with asymptomatic CAD comparing warfarin plus aspirin to aspirin

alone, all were in the setting of a recent acute coronary syndrome, and a number had only short-term follow-up. It is unknown whether the response to warfarin therapy, particularly with respect to bleeding, might differ in patients with symptomatic CAD vs symptomatic PAD. Therefore, we used only RCTs specifically enrolling patients with symptomatic PAD for our evaluation of warfarin therapy.

For the comparison of warfarin plus aspirin vs aspirin alone for nonfatal vascular outcomes, we used the event rates from participants taking aspirin in a meta-analysis of 16 RCTs evaluating aspirin use vs no aspirin use in patients with vascular disease adjusted to a 5-year time interval as our baseline risk estimate.[10] Because this meta-analysis does not provide data on total mortality or nonfatal major extracranial bleeds, we derived baseline risk estimates from the aspirin arm in the CHARISMA trial (total mortality) and CAPRIE trial (major nonfatal extracranial bleeding events).[15,18]

We identified three RCTs evaluating warfarin (international normalized ratio, 2.0-3.0) plus aspirin vs aspirin alone in 3,048 patients with established PAD.[19-21] Table 2 and Table S6 provide details about the quality of evidence and findings from our meta-analysis of the three included studies. Results failed to demonstrate or exclude an effect of warfarin plus aspirin vs aspirin alone on mortality, nonfatal MI, or nonfatal stroke. However, there was a significant increase in major bleeding events with warfarin plus aspirin compared with aspirin alone. The overall quality of evidence is low.

Recommendation

3.1-3.4. For secondary prevention in patients with symptomatic PAD, we recommend one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A). **We suggest *not to use* dual antiplatelet therapy with aspirin plus clopidogrel** (Grade 2B). **We recommend *not to use* an antiplatelet agent with moderate-intensity warfarin** (Grade 1B).

4.0 ANTITHROMBOTIC THERAPY FOR THE MANAGEMENT OF PATIENTS WITH CLAUDICATION

In the previous section, we recommended aspirin or clopidogrel for the prevention of nonfatal MI, nonfatal stroke, or vascular death for all patients with symptomatic PAD. In this section, we evaluate other therapies with antiplatelet and antithrombotic properties (eg, cilostazol, pentoxifylline, prostanoids) for their effect on quality of life. Unfortunately, most studies have not evaluated quality of life as an outcome

directly and often used walking distance as a surrogate. We make inferences regarding quality of life based on these data, inferences that are less certain because of indirectness. Because these therapies have not been shown to have an impact on cardiovascular events, they are considered only as possible additions to previously recommended antiplatelet treatments.

Patients with intermittent claudication have lower-extremity discomfort with walking, thereby limiting activity. In general, claudication itself is not associated with limb loss and is responsive to smoking cessation and exercise therapy. Cessation of tobacco use can significantly reduce lower-extremity symptoms and progression of PAD.[22,23] One systematic review suggested that structured exercise programs can improve maximal walking distance (MWD).[24] Therefore, additional drug therapy should be considered only in patients who have troubling limitations even after smoking cessation and exercise therapy.

Selection of Baseline Risk

For the three comparisons of cilostazol, pentoxifylline, and prostanoids vs placebo, because controlled trials showed large improvements in walking test distance in patients in placebo groups, for the surrogate outcome of MWD, we used a control response rate of 80%; that is, we assumed that 80% of untreated patients would show improvements in quality of life. We calculated the standardized mean differences, and when needed, we imputed SDs from other trials. We then converted standardized mean differences into risk differences[25,26] and present the results as the proportion of patients who experience an important benefit in quality of life (inferred from MWD). For evaluation of bleeding risk associated with cilostazol compared with no cilostazol or placebo, we used the control group risk estimate from a systematic review of 10 RCTs evaluating cilostazol in addition to dual antiplatelet therapy in coronary percutaneous transluminal angioplasty (PTA) and stenting.[27]

4.1 Cilostazol

Cilostazol is a phosphodiesterase III inhibitor of platelet activation and relaxes vascular smooth muscle. Ten RCTs that compared cilostazol 100 mg bid to placebo have been located in two systematic reviews.[28,29] Pooling data from seven studies comparing cilostazol vs placebo suggested that regarding health-related quality of life (as inferred from MWD), patients receiving cilostazol are more likely to experience an important benefit than those receiving placebo (79 more per 1,000 [55 more to 100 more]) (Table 3, Table S7). Changes in quality of life were evaluated directly in four of the studies

Table 2—[Section 3.1-3.4] Summary of Findings: Moderate-Intensity Warfarin (INR 2.0-3.0) Plus Aspirin vs Aspirin Alone for Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD[20,21,22]

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects Over 5 y	
				Risk With Aspirin	Risk Difference With Warfarin + Aspirin (95% CI)
Total mortality	3,048 (3 RCT), 35-60 mo	Low due to imprecision[a] and inconsistency[b]	RR 1.11 (0.79-1.55)	120 per 1,000[c]	13 more per 1,000 (from 25 fewer to 66 more)
MI nonfatal events	3,048 (3 RCT), 35-60 mo	Moderate due to imprecision[a]	RR 0.95 (0.64-0.1.41)	80 per 1,000[d]	4 fewer per 1,000 (from 28 fewer to 32 more)
Stroke, including nonfatal ischemic and hemorrhagic strokes[e]	3,048 (3 RCT), 35-60 mo	Moderate due to imprecision[a]	RR 0.92 (0.64-1.33)	110 per 1,000[d]	8 fewer per 1,000 (from 39 fewer to 36 more)
Major extracranial bleed nonfatal events	2,994 (2 RCT), 35-60 mo	High	RR 2.39 (1.50-3.82)	40 per 1,000[f]	55 more per 1,000 (from 20 more to 112 more)
Burden of treatment	N/A[g]	High	Warfarin > aspirin	Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits[d]	Aspirin: daily medication only

CAPRIE = Clopidogrel vs Aspirin in Patients at Risk for Ischemic Events; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; INR = international normalized ratio; N/A = not applicable; RCT = randomized controlled trial; RR = risk ratio. See Table 1 legend for expansion of other abbreviations.

[a]The 95% CI for absolute effect includes benefit and harm.

[b]Excess cancer deaths in one study with warfarin and aspirin.

[c]Control group risk estimates for total mortality come from the aspirin arm of the CHARISMA trial.

[d]Control group risk estimates for nonfatal MI and nonfatal stroke (ischemic, hemorrhagic, and unknown cause) come from observed events in a meta-analysis of 16 RCTs in secondary prevention.[11]

[e]Of total nonfatal strokes, two of 48 (4%) with aspirin and 17 of 50 (34%) with warfarin plus aspirin were hemorrhagic.

[f]Control group risk estimates for major bleeds come from the observed events in the aspirin-alone arm of the CAPRIE trial.[15]

[g]As far as we are aware, no studies have evaluated differences in burden of treatment between patients with PAD taking warfarin vs aspirin. There are studies evaluating quality of life in patients during warfarin treatment (with disparate findings), but these are limited by small sample size, lack of comparator, and other design issues.

Table 3—[Section 4.1-4.4] Summary of Findings: Cilostazol vs Placebo in Patients With Symptomatic PAD and Claudication[28]

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk Without Cilostazol	Risk Difference With Cilostazol (95% CI)
Total mortality	1,439 (1 RCT[30]), 34 mo	Low due to bias[a] and imprecision[b]	RR 0.94 (0.64-1.39)	68 per 1,000[c]	4 fewer per 1,000 (from 27 fewer to 26 more)
MI nonfatal events	...	...	...	...	...
Stroke, including nonfatal ischemic and hemorrhagic strokes	...	...	...	...	...
Major extracranial bleed	2,273 (6 RCT), 1-6 mo	Low due to indirectness[d] and inconsistency[e]	RR 0.89 (0.46-1.73)	44 per 1,000[c]	5 fewer per 1,000 (from 24 fewer to 32 more)
Quality of life as inferred from maximum walking distance (important outcome)	1,890 (7 RCT), 3-6 mo	Low due to bias,[f] inconsistency[g] and indirectness[h]	1.09 (1.06-1.12)	800 per 1,000	79 more per 1,000 (55 more to 100 more)[i]

See Table 1 and 2 legends for expansion of abbreviations.

[a]Unclear concealment of allocation.

[b]CI includes important benefit and harm; only 101 events.

[c]Control group risk estimates come from observed events reported in placebo arms of included studies.

[d]Data from studies comparing cilostazol vs placebo in addition to aspirin and clopidogrel following percutaneous coronary intervention.

[e]CIs include protective effect and harm.

[f]Unclear concealment of allocation in four of seven studies.

[g]Moderate heterogeneity (I^2 = 69%).

[h]Use of surrogate end point (walking distance for quality of life).

[i]Calculated from pooled standardized mean differences, converted into risk difference (assumed control response rate of 80%).

comparing cilostazol 100 mg bid to placebo.[31-34] All four trials reported results consistent with our inferences from MWD: a significant improvement in the physical health subscale of the SF-36 (Short Form Health Survey), suggesting an improvement in overall physical function. However, the overall health-related quality of life was not improved, with no changes in the mental health components (eg, social functioning, role-emotional subscale). In the largest of the trials, the results failed to demonstrate or exclude an effect of cilostazol on total mortality.[30]

Regarding quality of life (as inferred from MWD), patients receiving cilostazol 100 mg bid were more likely to experience an important benefit than those receiving pentoxifylline.[35] There were no significant differences in total mortality or adverse events (any adverse event or serious adverse events).

A separate review of a pharmaceutical safety database included eight RCTs of patients with symptomatic PAD.[36] The authors did not list the individual trials included in this database. There were 1,374 participants randomized to cilostazol (475 patient-years exposure) and 973 randomized to placebo (357 patient-years exposure). Although a formal meta-analysis does not appear to have been undertaken, the review reported no difference in rates of MI (1.0% vs 0.8%), stroke (0.5% vs 0.5%), or death (0.6% vs 0.5%) between patients with symptomatic PAD taking cilostazol or those taking placebo.[36] Major or minor bleeding rates were not reported.

As we considered whether to add cilostazol to existing antithrombotic therapy, we relied on bleeding data from studies comparing cilostazol to no cilostazol in patients undergoing coronary stenting (and already taking aspirin and clopidogrel) to estimate bleeding risk associated with this therapy. A systematic review of cilostazol in patients undergoing percutaneous coronary intervention included 10 RCTs (2,809 patients) comparing triple therapy with aspirin, clopidogrel, and cilostazol to aspirin plus clopidogrel.[27] Results failed to demonstrate or exclude an effect of cilostazol on major bleeding (risk ratio [RR], 0.89; 95% CI, 0.46-1.73).

4.2 Pentoxifylline

Pentoxifylline was compared with placebo in six small RCTs in patients with intermittent claudication. A pooled analysis of these trials failed to demonstrate a difference between pentoxifylline and placebo in quality of life as inferred from MWD (31 more per 1,000 [47 less to 94 more]).[29] Pentoxifylline was associated with more adverse events (96 more per 1,000 [21 more to 181 more]). The studies included had limitations in design and execution and showed marked variability, and there was

an important risk of publication bias; thus, the overall quality of the evidence was deemed to be low.

4.3 Heparins (Including Low-Molecular Weight Heparins)

A Cochrane systematic review of the use of heparin products in patients with intermittent claudication[37] identified five eligible studies (Table S8).[38-42] In the pooled data, there were no deaths, no bleeding events, and nine cardiovascular events with no significant differences between heparins and placebo. Effects of heparin on walking distance were only evaluable from one RCT in which heparin 12,500 units subcutaneously daily or placebo were administered for two 3-month periods followed by 6 months of observation in a crossover design. Aspirin was administered throughout the 18-month period.[38] Results failed to establish or exclude benefit or harm from heparin (112 more with improvement in quality of life per 1,000 [58 fewer to 149 more]) (Table S8).

4.4 Prostanoids

Prostaglandins (prostaglandin E1, prostaglandin I2, and their derivatives) are potent inhibitors of platelet activation, adhesion, and aggregation and have vasodilatory and antithrombotic effects. A meta-analysis of five studies (1,636 patients) suggested that with regard to quality of life as inferred from MWD, patients receiving prostaglandins are more likely to experience an important benefit than those receiving placebo (79 more per 1,000 [58 more to 98 more]) but have a higher risk of adverse events (RR, 2.61; 95% CI, 1.40-4.85).[43] There was substantial heterogeneity between study results ($I^2 = 64\%$). Results failed to demonstrate or exclude an effect of prostaglandins vs placebo on nonfatal stroke, nonfatal MI, revascularization, or death. The overall quality of the evidence is low due to risk of bias and imprecision and for quality of life, indirectness (Table S9).

Recommendation

4.1-4.4. For patients with intermittent claudication refractory to exercise therapy and smoking cessation, we suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C)**; we suggest against the use of pentoxifylline, heparinoids, or prostanoids** (Grade 2C)**.**

5.0 Critical Limb Ischemia

Patients with critical limb ischemia have inadequate resting blood flow to the lower limbs, resulting

in rest pain, ulceration, and eventually gangrene and limb loss. Such patients are candidates for prompt revascularization. Pertinent outcomes include relief of pain, quality of life, and limb salvage.

5.1 Prostanoids

Investigators have also administered prostaglandins to patients with critical limb ischemia in hopes of relieving rest pain and healing ischemic ulcers. A Cochrane systematic review identified 13 studies comparing prostanoids to placebo in patients with critical limb ischemia without chance of rescue or reconstructive intervention.[44] These studies measured outcomes in different ways. The authors of the review dealt with this variability by dichotomizing the continuous results. Pain relief was defined as any improvement on a validated pain scale. Ulcer healing was defined as any decrease in lesion surface area and presence of granulation tissue. The overall quality of the evidence is low because of limitations in design, imprecision, and inconsistency.

Prostanoids improved rest pain and ulcer healing (77 and 136 patients per 1,000 treated, respectively) but did not significantly prevent amputations or decrease mortality (Table 4, Table S10). Prostanoids were poorly tolerated, with ~75% of subjects experiencing at least one adverse event compared with 31% of controls (the most commonly reported adverse effects were headache, nausea, vomiting, diarrhea, and facial flushing). A sensitivity analysis restricted to the eight highest-quality studies found similar results with respect to the five outcome variables.

Recommendation

5.1. For patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention, we suggest the use of prostanoids in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C)**.**

Values and preferences: Patients who do not value uncertain relief of rest pain and ulcer healing greater than avoidance of a high likelihood of drug-related side effects will be disinclined to undergo prostanoid therapy.

6.0 ACUTE LIMB ISCHEMIA

Acute limb ischemia results from a sudden interruption of blood flow to an extremity.[45] The most common causes of nontraumatic acute arterial occlusion are embolism and thrombosis.[45-47] Approximately 80% of peripheral emboli originate in the heart (eg, left atrial appendage, left ventricular apex, native and prosthetic cardiac valves). In the remaining cases, emboli originate from the aorta or peripheral vessels themselves or are of venous origin (paradoxical with migration through patent foramen ovale and atrial septal defect). Thrombotic occlusion is most commonly associated with advanced atherosclerosis, with slow progression of disease.[47] The limb typically has developed a collateral blood supply, and the final occlusion of the stenotic vessel often is not immediately limb threatening.[45,47]

6.1 Anticoagulation for Acute Limb Ischemia

Regardless of the cause and level of acute limb ischemia, patients usually receive short-term anticoagulation treatment with therapeutic doses of heparin to reduce the extent of ischemic injury by preventing clot propagation and further embolism. Although the logic of this approach is widely accepted, there are no formal studies demonstrating improved outcomes with anticoagulation. The expected adverse effect of preoperative anticoagulant therapy is an increased risk of bleeding, including wound hematomas. To our knowledge, there are no randomized trials directly comparing unfractionated heparin with other anticoagulants in this setting.

6.2 Thrombolysis vs Surgery for Acute Limb Ischemia

Treatment of acute limb ischemia is directed at restoration of flow to the occluded artery, which is now commonly accomplished by either surgery or catheter-directed intraarterial thrombolysis. Although no formal data support either reperfusion therapy over anticoagulation alone or supportive care, the high risk of limb loss (and subsequent associated morbidity and mortality) without blood flow restoration has led to widespread use of both modalities.

Table 5 and Table S11 summarize the results from a meta-analysis that provides the best evidence regarding the comparative benefits and harms of intraarterial thrombolysis vs surgery.[48] This meta-analysis presented data from five randomized trials of 1,180 patients.[49-53] We provide absolute effect estimates based on control (surgical arm) event rates from these trials. In summary, thrombolysis compared with surgery appeared to have little or no effect on limb salvage but was associated with an increase risk in stroke (10 per 1,000 treated) and major bleeding (16 per 1,000 treated) at 30 days. Results failed to demonstrate or exclude an effect of thrombolysis vs surgery on amputation or death. We consider the overall quality of evidence to be moderate because of inconsistency and imprecision.

Table 4—[Section 5.1] Summary of Findings: Prostanoids vs Placebo in Patients With Critical Limb Ischemia Ineligible for Revascularization[44]

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk Without Prostanoids	Risk Difference With Prostanoids (95% CI)
Total mortality	1,391 (5 RCT), 32 wk	Low due to risk of bias,[a] inconsistency,[b] and imprecision[c]	RR 1.07 (0.65-1.75)	121 per 1,000[d]	8 more per 1,000 (from 42 fewer to 90 more)
MI nonfatal events	...	...	...	...	...
Stroke, including nonfatal ischemic and hemorrhagic strokes	...	...	...	...	...
Major extracranial bleed	...	...	...	...	...
Rest pain relief (any improvement on validated scale)	1,116 (9 RCT), 21.4 wk	Moderate due to risk of bias[a]	RR 1.32 (1.1-1.57)	243 per 1,000[d]	77 more per 1,000 (from 24 more to 138 more)
Ulcer healing (any decrease in size or granulation tissue)	1,132 (8 RCT), 17.5 wk	Low due to risk of bias[a] and inconsistency[e]	RR 1.54 (1.22-1.96)	253 per 1,000[d]	136 more per 1,000 (from 55 more to 242 more)
Amputations (major or minor amputations)	1,790 (9 RCT), 23.1 wk	Low due to risk of bias[a] and imprecision[f]	RR 0.89 (0.76-1.04)	313 per 1,000[d]	34 fewer per 1,000 (from 75 fewer to 12 more)
Adverse events	716 (8 RCT), 14.4 mo	Moderate due to risk of bias[a]	RR 2.35 (1.99-2.78)	77 per 1,000[g]	103 more per 1,000 (from 76 more to 137 more)
				394 per 1,000[g]	531 more per 1,000 (from 390 more to 701 more)

See Table 1 and 2 legends for expansion of abbreviations.

[a]Unclear allocation of concealment and blinding concerns.

[b]$I^2 = 40\%$.

[c]CIs include both important benefit and harm. Small number of events (145).

[d]Control group risk estimates come from median control group rates or representative control group risk of the included studies.

[e]$I^2 = 44\%$.

[f]CIs include important benefit and harm.

[g]Representative control group risk.

Table 5—[Section 6.1-6.3] Summary of Findings: Thrombolysis vs Surgery for the Treatment of Acute Limb Ischemia[48]

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With Surgery	Risk Difference With Thrombolysis (95% CI)
Total mortality at 1 y[a]	768 (3 RCTs),[b] 12 mo	Low due to imprecision[c] and inconsistency[d]	RR 0.74 (0.35-1.58)	169 per 1,000[e]	43 fewer per 1,000 (from 109 fewer to 98 more)
MI nonfatal events	...	...	...	...	...
Strokes at 30 d includes nonfatal ischemic and hemorrhagic strokes[f]	1,180 (5 RCTs),[b,g] 1-12 mo	Moderate due to imprecision[h]	0.01 (0.00-0.02)[i]	0 per 1,000[e]	10 more per 1,000 (from 0 fewer to 20 more)
Major extracranial bleed at 30 d	1,070 (4 RCTs),[b] 1-12 mo	Moderate due to imprecision[j]	RR 2.34 [1.32-4.14]	12 per 1,000[e]	16 more per 1,000 (from 3 more to 37 more)
Limb salvage at 1 y	654 (2 RCTs),[b] 12 mo	Low due to imprecision[c] and inconsistency[k]	RR 1.00 (0.86-1.17)	754 per 1,000[e]	0 fewer per 1,000 (from 106 fewer to 128 more)
Amputation at 1 y	768 (3 RCTs),[a] 12 mo	Moderate due to imprecision[c]	RR 1.10 (0.88-1.38)	190 per 1,000[e]	19 more per 1,000 (from 22 fewer to 72 more)

See Table 1 and 2 legends for expansion of abbreviations.

[a]Ouriel et al[48] reported that one of 54 deaths in the thrombolysis group was from intracranial hemorrhage, whereas none of 46 in the surgery group were from intracranial hemorrhage.

[b]For one study using three different doses of the thrombolytic agent, only the optimal dose is used for comparison with surgery. Control group risk estimates come from control event rates in the median study (after arranging risks in increasing order).

[c]The 95% CI for absolute effect includes important benefit and harm.

[d]$I^2 = 80\%$.

[e]Control risk estimates from median or representative control group risk of included studies.

[f]Of reported nonfatal strokes, all happened in the thrombolysis group, and all were intracranial hemorrhages (eight of eight [100%]).

[g]Weaver et al[53] included patients with both acute and chronic limb ischemia.

[h]The 95% CI for absolute effect includes important benefit and harm; low number of events (eight).

[i]Pooled risk difference presented instead of relative risk.

[j]The 95% CIs are wide, low number of events (60).

[k]$I^2 = 49\%$.

Antithrombotic Therapy in Peripheral Artery Disease

6.3 Comparison of Intraarterial Thrombolytic Agents for Acute Limb Ischemia

In the past, thrombolysis for acute limb ischemia was administered by IV; now this strategy has been replaced by catheter-directed thrombolysis. Evidence comparing the efficacy of different intraarterial thrombolytic agents for acute limb ischemia is limited. However, in a Cochrane systematic review, Robertson et al[54] identified four randomized trials comparing recombinant tissue-type plasminogen activator (rt-PA), urokinase, or streptokinase for the management of acute lower-limb ischemia.[55-58] Included was one small RCT comparing intraarterial streptokinase to intraarterial rt-PA in 40 patients with acute limb ischemia.[55] With streptokinase, there was an increased rate of amputation at 30 days (seven of 20 vs one of 20; RR, 7.0; 95% CI, 0.95-51.80). Results failed to demonstrate or exclude an effect of streptokinase vs intraarterial rt-PA on asymptomatic limb salvage, major hemorrhage, or death.

Initially, streptokinase was the most widely used agent, but since this study[55] and because of other safety concerns (eg, allergic reactions), it has largely been replaced by urokinase and rt-PA.[54] Three RCTs compared intraarterial urokinase to rt-PA for acute peripheral arterial occlusion.[56-58] The overall quality for this comparison is low because of imprecision in outcome estimates as well as limitations in design and execution. Results failed to demonstrate or to exclude an effect of intraarterial rt-PA vs intraarterial urokinase on amputation, limb salvage, major hemorrhage, or death (Table S12).

Recommendation

6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C)**; we suggest reperfusion therapy (surgery or intraarterial thrombolysis) over no reperfusion therapy** (Grade 2C)**; and we recommend surgery over intraarterial thrombolysis** (Grade 1B)**. In patients undergoing intraarterial thrombolysis, we suggest rt-PA or urokinase over streptokinase** (Grade 2C)**.

7.0 Endovascular Revascularization in Patients With Symptomatic PAD

Patients with refractory claudication, rest pain, and ischemia often require revascularization for symptomatic relief and limb salvage. Increasingly, patients are undergoing PTA with or without stent placement. Few studies guide clinicians regarding type and duration of antithrombotic therapy following such proce-

dures. Current practice is very heterogeneous and often is based on indirect evidence from studies in patients undergoing coronary stenting.

7.1 Antithrombotic Therapy Following PTA With and Without Stent Procedures

A Cochrane review[59] pooled data from two early studies, including 356 patients undergoing lower-extremity PTA without stent placement, and found a possible reduction in reocclusion at 6 months in patients taking aspirin plus dipyridamole compared with placebo (OR, 0.69; 95% CI, 0.44-1.10).[60,61] Two other studies failed to demonstrate or exclude an effect of aspirin and dipyridamole vs phenprocoumon (vitamin K antagonist) in reocclusion at 6 months following PTA (OR, 0.78; 95% CI, 0.43-1.41).[62,63] One study failed to demonstrate or exclude an effect on 12-month reocclusion in patients taking ticlopidine compared with phenprocoumon (OR, 0.71; 95% CI, 0.37-1.36).[64] An additional study randomized 179 patients following PTA (pelvic or lower extremity) complicated by extensive dissection to IV unfractionated heparin vs subcutaneous nadroparin (a low-molecular-weight heparin) administered for 1 week postprocedure (followed by 6 months of aspirin in each arm).[65] Nadroparin was associated with a reduction in vessel restenosis/occlusion at 6 months (OR, 0.35; 95% CI, 0.19-0.65) but failed to demonstrate or exclude an effect on amputation (OR, 1.0; 95% CI, 0.20-5.10).

We have identified no RCTs comparing antithrombotic agents post-PTA with stent placement. Indeed, it remains unclear whether PTA with stent placement is superior to PTA alone with respect to patient-important outcomes. In a recent meta-analysis of 10 RCTs, PTA plus routine stenting for superficial femoropopliteal arterial disease was associated with a possible reduction in restenosis (RR, 0.85; 95% CI, 0.69-1.06) compared with PTA without routine stenting but failed to demonstrate or exclude an effect on need for target vessel revascularization (RR, 0.98; 95% CI, 0.78-1.23).[66]

Nevertheless, stenting is performed frequently. Despite low-quality evidence regarding thienopyridines in patients undergoing PTA with stent placement for PAD, many interventionists provide a loading dose of clopidogrel in addition to aspirin preprocedure and then continue dual antiplatelet therapy for 1 to 3 months post-PTA (particularly if a stent is placed in a small peripheral vessel). The rationale for this practice is based on the results from coronary artery stenting trials (see section 3 of Vandvik et al[4] in this supplement).

We are skeptical about extrapolating these data to all patients with PAD given differences in the

risk of stent thrombosis (lower in stenting of larger-caliber peripheral arteries compared with smaller coronary arteries), difference in stent types, and differing outcomes related to stent thrombosis (limb ischemia vs MI). Furthermore, dual antiplatelet therapy is associated with an increased risk of major bleeding compared with single antiplatelet therapy (see sections 2 and 3 of Vandvik et al[4] in this supplement).

Recommendation

7.1. For patients undergoing peripheral artery PTA with or without stenting, we recommend long-term aspirin (75-100 mg/d) or clopidogrel (75 mg/d) (Grade 1A). **For patients undergoing peripheral artery PTA with stenting, we suggest single rather than dual antiplatelet therapy** (Grade 2C).

Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a potential increased risk of bleeding are likely to choose to use dual antiplatelet therapy.

8.0 Antithrombotic Therapy Following Peripheral Artery Bypass Graft Surgery

In this section, we review evidence from studies evaluating antithrombotic therapy following peripheral bypass surgery. For the most part, these data do not suggest that recommendations for antithrombotic therapy following peripheral artery bypass surgery should differ from that in other patients with symptomatic PAD. One exception is the use of dual antiplatelet therapy in patients following prosthetic graft bypass surgery.

Selection of Baseline Risk Estimate

For the comparison of warfarin vs aspirin or clopidogrel plus aspirin vs aspirin following PAD surgery, we used as our baseline risk estimate the event rates from patients receiving aspirin in the Dutch Bypass Oral Anticoagulants or Aspirin (BOA) study normalized to 1 year.[67] For the comparison of aspirin plus dipyridamole vs placebo, we calculated baseline risk estimates in the placebo group by applying the relative risk for placebo vs aspirin plus dipyridamole to the aforementioned aspirin baseline risk estimate.[68]

8.1 Aspirin and Dipyridamole vs Placebo

We used the data from the Cochrane review of six RCTs with a total of 966 patients[69-74] by Brown et al[68]

that evaluated the impact of aspirin and dipyridamole vs placebo in patients postinfrainguinal (venous or prosthetic) bypass graft surgery (for refractory claudication and limb salvage). The relative effects of aspirin plus dipyridamole vs aspirin alone have not been evaluated.

The overall quality of the evidence is low because of indirectness (loss of graft patency being a surrogate for amputation) and bias (Table 6, Table S13). Aspirin plus dipyridamole may result in 22 fewer graft occlusions per 1,000 patients (32 fewer to 12 fewer) treated for 12 months. Only one study provided data on amputation rates wherein aspirin plus dipyridamole compared with placebo for 12 months was associated with a possible reduction in amputations (34 fewer amputations per 1,000 patients treated [51 fewer to one more]). Pooled data from three studies reporting other vascular outcomes suggested that treatment with aspirin plus dipyridamole was associated with a possible reduction in nonfatal MI but failed to demonstrate or exclude an effect on nonfatal stroke. Aspirin plus dipyridamole was associated with a possible increase in bleeding (eight more major bleeding events per 1,000 treated [one fewer to 30 more]).

8.2 Aspirin With or Without Dipyridamole vs Other Agents

The same Cochrane review presented evidence from studies comparing aspirin with or without dipyridamole to other agents.[68] These other agents included low-molecular-weight heparin, indobufen, pentoxifylline, and prostaglandins. All these studies failed to demonstrate or exclude an effect of these agents compared with aspirin with or without dipyridamole in long-term graft patency or major extracranial bleeding. Individual studies were underpowered for assessment of treatment differences in MI, stroke, or mortality.

8.3 Clopidogrel Plus Aspirin vs Aspirin Alone

The Clopidogrel and Acetylsalicyclate Acid in Bypass Surgery for Peripheral Arterial Disease (CASPAR) study randomized 851 patients undergoing unilateral below-knee bypass graft surgery for PAD to clopidogrel (75 mg/d) plus aspirin (75-100 mg/d) vs placebo plus aspirin.[75] In the overall cohort, aspirin and clopidogrel failed to demonstrate or exclude an effect on limb amputation, nonfatal extracranial bleeding, or total mortality compared with aspirin alone (Table S14).

Randomization of patients in this trial was stratified according to graft type (venous or prosthetic), and the investigators undertook prespecified analysis of these subgroups. In the subgroup of patients

Table 6—[Section 8.1-8.3] Summary of Findings: Aspirin Plus Dipyridamole vs Placebo for Prevention of Thrombosis After Peripheral Bypass Surgery

Outcomes	Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects Over 1 y	
				Risk Without Aspirin	Risk Difference With Aspirin (95% CI)
Total mortality	750 (3 RCTs), 12 mo	Moderate due to imprecision[a]	RR 0.86 (0.6-1.22)	105 per 1,000[b]	14 fewer per 1,000 (from 42 fewer to 23 more)
MI nonfatal events	667 (3 RCTs), 12 mo	Moderate due to imprecision[c]	RR 0.65 (0.4-1.06)	28 per 1,000[b]	9 fewer per 1,000 (from 16 fewer to 1 more)
Stroke,[d] including nonfatal ischemic and hemorrhagic strokes	667 (3 RCTs), 12 mo	Moderate due to imprecision[a]	RR 0.79 (0.42-1.49)	27 per 1,000[b]	5 fewer per 1,000 (from 15 fewer to 13 more)
Major extracranial bleed[e]	598 (2 RCTs), 12 mo	Moderate due to imprecision[f]	RR 1.86 (0.85-4.04)	10 per 1,000[b]	8 more per 1,000 (from 1 fewer to 30 more)
Amputation	148 (1 RCTs), 12 mo	Low due to risk of bias[g] and imprecision[c]	RR 0.52 (0.27-1.01)	71 per 1,000[b]	34 fewer per 1,000 (from 51 fewer to 1 more)
Amputation inferred from loss of graft patency	966 (6 RCTs), 12 mo	Low due to risk of bias[g] and indirectness[h]	RR 0.68 (0.55-0.83)	71 per 1,000[b]	22 fewer per 1,000 (from 32 fewer to 12 fewer)

See Table 1 and 2 legends for expansion of abbreviations.

[a]The 95% CIs include important benefit and harm.

[b]Control group risk estimate derived from application of relative risk of placebo vs aspirin/dipyridamole to aspirin event rate in a large RCT (BOA [Dutch Bypass Oral anticoagulants or Aspirin study]) comparing warfarin to aspirin following peripheral artery bypass surgery.[61]

[c]The 95% CIs include important benefit and no benefit.

[d]None of the strokes was due to intracranial hemorrhage.

[e]Of these bleeds, five of 19 (26%) were GI.

[f]The 95% CIs include no benefit and important harm.

[g]Problems with allocation concealment, blinding.

[h]Graft patency is surrogate for amputation.

undergoing venous graft bypass (n = 598), there were no significant differences in the rates of amputation, major bleeding, or death between the two treatment arms. However, in the subgroup of patients undergoing prosthetic graft bypass (n = 253), there was a significant decrease in amputations in patients treated with clopidogrel plus aspirin (24 per 1,000 treated; 95% CI, 35 fewer to three fewer; $P = .008$ using the Wald test for interaction) (Table S15). The substudy analysis failed to demonstrate or exclude an effect of clopidogrel and aspirin on total mortality or major extracranial bleeding. The quality of this evidence is considered low given very serious imprecision.

8.4 Oral Anticoagulants vs Antiplatelet Agents

The BOA study randomized 2,650 patients who had undergone infrainguinal bypass grafting to either high-intensity oral anticoagulation (with phenprocoumon or acenocoumarol [target international normalized ratio, 3-4.5]) or aspirin.[67] Table S16 provides a review of the evidence and quality of this study. This study failed to demonstrate or exclude an effect of oral anticoagulation vs aspirin on all-cause mortality, nonfatal stroke, or limb loss. Although associated with a possible reduction in nonfatal MI, there was a significant increase in extracranial major bleeding events in the oral anticoagulation group.

Warfarin Plus Aspirin vs Warfarin Alone: Two studies compared warfarin plus aspirin to aspirin alone in patients after lower-limb surgical bypass.[19,20] Both studies were included in the previous evaluation of the comparison of warfarin plus aspirin vs aspirin alone in patients with symptomatic PAD (see section 3).

In summary, the quality of the evidence for antiplatelet and antithrombotic therapy following PAD surgery for patient-important outcomes, such as amputation, limb loss, and mortality is low to moderate. Aspirin plus dipyridamole was associated with a possible reduction in amputation compared with placebo, but no comparison with aspirin alone has been performed. We did not identify any studies comparing aspirin alone to no aspirin. Aspirin plus clopidogrel was associated with a decrease in amputations over aspirin alone in a subgroup of patients undergoing prosthetic graft placement in one study.[75] Warfarin with or without aspirin is associated with a significant increase in extracranial bleeding compared with aspirin alone. The impact of these therapies on other critical vascular outcomes (nonfatal MI or stroke) cannot be adequately assessed based on these studies. With the exception of a weak recommendation for clopidogrel plus aspirin for 1 year

in patients undergoing below-knee prosthetic graft placement, our recommendations for long-term antithrombotic therapy following peripheral bypass surgery are the same as those for other patients with symptomatic PAD (see section 2).

Recommendation

8.1-8.4. We recommend one of the following antithrombotic regimens to be continued long term in most patients following peripheral artery bypass graft surgery over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A)**. We recommend single antiplatelet therapy over antiplatelet therapy and warfarin** (Grade 1B)**. In patients undergoing below-knee bypass graft surgery with prosthetic grafts, we suggest clopidogrel 75 mg/d plus aspirin (75-100 mg/d) over aspirin alone for 1 year** (Grade 2C)**. For all other patients, we suggest single over dual antiplatelet therapy** (Grade 2B)**.

9.0 CAROTID ARTERY STENOSIS

Carotid stenosis may coexist in asymptomatic patients as well as in symptomatic patients with CAD or PAD. Recent prevalence estimates range from 0.2% in men aged < 50 years to 7.5% in men aged ≥ 80 years.[76]

9.1 Primary Prevention of Cardiovascular Events

As with patients with asymptomatic PAD, we consider the evidence for aspirin therapy for the primary prevention of vascular events and total mortality described in Vandvik et al[4] applicable to patients with asymptomatic carotid stenosis (Table S2). Patients with asymptomatic carotid stenosis may be stratified into low, moderate, or high risk for vascular events as described in section 2 of the cited article. Our recommendations for primary prevention in patients with asymptomatic carotid stenosis, therefore, are identical to those for patients with asymptomatic PAD or at risk for CAD. Section 1.2 of Vandvik et al[4] in this supplement provides a more-detailed discussion of the evidence.

9.2 Antithrombotic Therapy for Secondary Prevention in Patients With Symptomatic Carotid Stenosis

The article by Lansberg et al[77] in this supplement provides a full description of the evidence and recommendations for antithrombotic therapy for secondary prevention in patients with symptomatic carotid stenosis. Recommendations are repeated here for readers' ease of use.

9.3 Antithrombotic Therapy for Secondary Prevention in Patients Following Carotid Endarterectomy

We believe that the evidence for patients with symptomatic carotid stenosis also applies to patients following carotid endarterectomy (even if previously asymptomatic). Therefore, recommendations for therapy following carotid endartectomy are the same as for patients with symptomatic carotid stenosis.

There are no studies evaluating timing of initiation of antithrombotic therapy before or after endarterectomy. For recommendations regarding continuation and discontinuation of antithrombotic therapy and timing of reinitiation relative to surgery, see Douketis et al[78] in this supplement.

For completeness, we summarize the limited direct evidence for antiplatelet therapy in patients following carotid endarterectomy. A Cochrane systematic review identified six RCTs comparing antiplatelet therapy to no antiplatelet therapy in patients with symptomatic or asymptomatic carotid stenosis undergoing carotid endarterectomy (with ≥ 3 months of follow-up).[79] Four of the trials tested aspirin (dose range, 50-1,300 mg),[80-83] one trial tested aspirin (990 mg) plus dipyridamole (225 mg),[84] and one trial tested indobufen (400 mg).[85] Five of the six trials used placebo controls. Timing of initiation of antiplatelet therapy ranged from 12 h prior to carotid endarterectomy to up to 3 months after carotid endarterectomy; treatment and follow-up duration ranged from 6 to 54 months. Antiplatelet drugs were associated with a significant reduction in strokes (OR, 0.58; 95% CI, 0.34-0.98); the estimated absolute effect was 34 fewer per 1,000 patients treated (2 fewer to 54 fewer). Results failed to demonstrate or exclude an effect of antiplatelet therapy on vascular mortality, nonfatal MI, or nonfatal extracranial hemorrhages. Overall quality of the evidence is low because of risk of bias, imprecision, and inconsistency.

Previously presented data in patients with vascular disease suggested no benefit and probable increased harm associated with increasing aspirin doses (section 2 of Vandvik et al[4]). In addition, the Aspirin and Carotid Endarterectomy trial randomly assigned 2,849 patients scheduled for endarterectomy to one of four doses of aspirin (81, 325, 650, and 1,300 mg).[86] Aspirin was started before surgery and continued for 3 months. The combined rate of stroke, MI, and death was lower in the low-dose groups (81 and 325 mg) than in the high-dose groups at 30 days (5.4% vs 7.0%, $P = .07$) and at 3 months (6.2% vs 8.4%, $P = .03$). No RCTs measured patient-important outcomes comparing clopidogrel vs aspirin or clopidogrel plus aspirin vs single antiplatelet therapy in patients undergoing carotid endarterectomy.

Recommendations

9.1. For persons with asymptomatic carotid stenosis, we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis.

9.2-9.3. In patients with symptomatic carotid stenosis (including recent carotid endarterectomy), we recommend long-term antiplatelet therapy (clopidogrel [75 mg once daily] or aspirin-extended-release dipyridamole [25 mg/200 mg bid] or aspirin [75-100 mg once daily]) over no antiplatelet therapy (Grade 1A). **We suggest either clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg nid) over aspirin (75-100 mg/day)** (Grade 2B).

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Endorsements: This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.

Additional information: The supplement Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e669S/suppl/DC1.

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