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Official publication of the American College of Chest Physicians



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Chest 2008;133:815S-843S
DOI 10.1378/chest.08-0686

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http://www.chestjournal.org/content/133/6_suppl/815S.full.html

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Antithrombotic Therapy for Peripheral Artery Occlusive Disease*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Michael Sobel, MD; and Raymond Verhaeghe, MD

This chapter is devoted to antithrombotic therapy for peripheral artery occlusive disease as part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see the "Grades of Recommendation" chapter by Guyatt et al, *CHEST* 2008; 133:123S–131S). Among the key recommendations in this chapter are the following: We recommend lifelong antiplatelet therapy in comparison to no antiplatelet therapy in pulmonary artery disease (PAD) patients with clinically manifest coronary or cerebrovascular disease (Grade 1A), and also in those without clinically manifest coronary or cerebrovascular disease (Grade 1B). In patients with PAD and intermittent claudication, we recommend against the use of anticoagulants (Grade 1A). For patients with moderate to severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, we recommend cilostazol (Grade 1A). We suggest that clinicians not use cilostazol in those with less-disabling claudication (Grade 2A). In patients with short-term (< 14 days) arterial thrombosis or embolism, we suggest intraarterial thrombolytic therapy (Grade 2B), provided they are at low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization. For patients undergoing major vascular reconstructive procedures, we recommend IV unfractionated heparin (UFH) prior to the application of vascular cross clamps (Grade 1A). For all patients undergoing infrainguinal arterial reconstruction, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. For routine autogenous vein infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. For routine prosthetic infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. In patients undergoing carotid endarterectomy, we recommend that aspirin, 75–100 mg, be administered preoperatively and continued indefinitely (75–100 mg/d) [Grade 1A]. In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), we suggest that dual antiplatelet therapy with aspirin and clopidogrel be avoided (Grade 1B). For all patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin, 75–100 mg/d (Grade 1C).

(*CHEST* 2008; 133:815S–843S)

Key words: anticoagulation; antiplatelet therapy; aspirin; atherosclerosis; carotid artery; heparin; intermittent claudication; peripheral vascular disease; randomized controlled trial; review; thrombolysis; vascular surgery

Abbreviations: ACD = absolute claudication distance; CAD = coronary artery disease; CI = confidence interval; COM = Claudication Outcome Measures; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PAD = peripheral arterial disease; PTFE = polytetrafluoroethylene; QOL = quality of life; RCT = randomized controlled trial; SF-36 = Short Form-36; STILE = Surgery vs Thrombolysis for Ischemia of the Lower Extremity; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist; WIQ = Walking Impairment Questionnaire

1.0 Chronic Limb Ischemia and Intermittent Claudication

1.1.1.1. In PAD patients with clinically manifest coronary or cerebrovascular disease, we recommend lifelong antiplatelet therapy in comparison to no antiplatelet therapy (Grade 1A).

1.1.1.2. In those without clinically manifest coronary or cerebrovascular disease, we suggest aspirin (75–100 mg/d) over clopidogrel (Grade 2B). In patients who are aspirin intolerant, we recommend clopidogrel over ticlopidine (Grade 1B).

Values and preferences: This recommendation places a relatively high value on avoiding large expenditures to achieve uncertain, small reductions in vascular events.

1.1.2. In patients with PAD and intermittent claudication, we recommend against the use of anticoagulants to prevent vascular mortality or cardiovascular events (Grade 1A).

1.1.4. For patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, we recommend cilostazol (Grade 1A). We suggest that clinicians not use cilostazol in those with less-disabling claudication (Grade 2A). We recommend against the use of pentoxifylline (Grade 2B).

Values and preferences: Because of the cost of cilostazol therapy, and the safety and efficacy of an exercise program, we recommend cilostazol treatment be reserved for patients with moderate to severe claudication who have tried and failed an exercise program and are not candidates for vascular surgical or endovascular procedures.

1.1.5. For patients with intermittent claudication, we recommend against the use of anticoagulants (Grade 1A).

1.1.6. For patients with limb ischemia, we suggest clinicians do not use prostaglandins (Grade 2B).

2.1. In patients who suffer from acute arterial emboli or thrombosis, we recommend immediate systemic anticoagulation with UFH, over no anticoagulation (Grade 1C). In patients undergoing embolectomy we suggest following systemic anticoagulation with UFH with long-term anticoagulation with vitamin K antagonists (VKA) (Grade 2C).

2.2. In patients with short-term (< 14 days) thrombotic or embolic disease, we suggest intraarterial thrombolytic therapy (Grade 2B) pro-

vided patients are at low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization by this method.

Values and preferences: This recommendation places relatively little value on small reductions in the need for surgical intervention and relatively high value on avoiding large expenditures and possible major hemorrhagic complications.

3.1. For patients undergoing major vascular reconstructive procedures, we recommend IV UFH, prior to the application of vascular cross clamps (Grade 1A).

3.2. For all patients undergoing infrainguinal arterial reconstruction, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We recommend against the routine use of perioperative dextran, heparin, or long-term anticoagulation with VKAs for all extremity reconstructions (Grade 1B).

3.3. For patients receiving routine autogenous vein infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We suggest that VKAs not be used routinely in patients undergoing infrainguinal vein bypass (Grade 2B). For those at high risk of bypass occlusion and limb loss, we suggest VKAs plus aspirin (Grade 2B).

Values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

3.4. For patients receiving routine prosthetic infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We suggest that VKAs not be used routinely in patients undergoing prosthetic infrainguinal bypass (Grade 2A).

Values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

4.0. In patients undergoing carotid endarterectomy, we recommend that aspirin, 75–100 mg, be given preoperatively to prevent perioperative ischemic neurologic events. We recommend lifelong postoperative aspirin (75–100 mg/d) [Grade 1A].

5.0. In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), we recommend lifelong aspirin, 75–100 mg/d (Grade 1C). In this patient group, we recommend against dual antiplatelet therapy with aspirin and clopidogrel (Grade 1B).

6.0. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin (75–100 mg/d) [Grade 1C]. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend against anticoagulation with heparin or VKA (Grade 1A).

1.0 CHRONIC LIMB ISCHEMIA AND INTERMITTENT CLAUDICATION

The most common symptom of atherosclerotic peripheral arterial occlusive disease (PAD) is intermittent claudication. Among men over the age of 60 years, 2 to 3% have symptomatic PAD, as do 1 to 2% of women.^{1–3} However the prevalence of asymptomatic PAD, generally proven by a reduced ankle/brachial systolic pressure index, is three to four times as great.^{4,5} After 5 to 10 years, 70 to 80% of patients with symptomatic disease remain unchanged or improved, 20 to 30% have progression of symptoms and/or require intervention, and < 3% will require amputation.^{6–8} Progression of disease is greatest in patients with multilevel arterial involvement, low ankle-to-brachial pressure indexes, chronic renal insufficiency, diabetes mellitus and, possibly, heavy smoking.^{6,5}

The prevalence of PAD increases with age and PAD is a significant cause of hospital admission. The diagnosis of PAD is an important predictor of overall cardiovascular and stroke mortality, which is increased twofold to threefold.^{1,2,9,10} Rest pain and critical ischemia are usually the result of progression of atherosclerotic disease, leading to occlusion of the distal vessels such as the popliteal and tibial arteries. There is an inverse relationship between the ankle-to-brachial pressure index and clinically manifest cardiovascular disease.⁵ The lower the index, the greater the occurrence of adverse cardiac events, strokes, and cardiovascular deaths.

From studies of patients with PAD, and generalizing from trials in broader populations, there is good evidence that addressing key risk factors such as smoking, dyslipidemia, and hypertension, will reduce the mortality and morbidity of cardiovascular isch-

emic events.^{11–14} At the same time, there is a growing body of evidence that treatment of these modifiable risk factors is often neglected in PAD patients compared to cohorts that present with coronary artery disease (CAD) or stroke.^{12,15} This may explain, in part, why the results of antithrombotic therapy in PAD have not always been consonant with the results in other atherosclerotic populations.

Several excellent reviews of PAD have been published since this chapter was last written,^{16,17} and consensus practice guidelines have been authored by major national and international groups.^{8,18} In the preparation of our guidelines, we have consulted these as well as the primary source clinical trials.

1.1 Antiplatelet Therapy To Prevent Ischemic Cardiovascular Events and Death in Patients With PAD

Antithrombotic therapy may modify the natural history of chronic lower-extremity arterial insufficiency as well as lower the incidence of associated cardiovascular events. However, no convincing data from properly designed large trials demonstrate that antithrombotic therapy will delay or prevent progression of atherosclerosis itself.

A compelling reason to administer antiplatelet therapy to patients with PAD is to prevent death and disability from stroke and myocardial infarction (MI). The Antithrombotic Trialists' Collaboration meta-analysis¹⁹ found that among 9,214 patients with PAD in 42 trials there was a 23% reduction in serious vascular events ($p = 0.004$) in patients treated with antiplatelet therapy. Patients with intermittent claudication, those having peripheral bypass, endarterectomy, and those having peripheral angioplasty all benefited to a similar degree.

1.1.1 Aspirin

The Antiplatelet Trialists analysis showed that for all conditions, aspirin at 80 to 325 mg/d was at least as effective as any other regimen, including higher-dose aspirin therapy, which is more prone to cause side effects and GI complications.¹⁹ Data from a single randomized controlled trial (RCT) suggests that aspirin, alone or combined with dipyridamole, will delay the progression of established arterial occlusive disease as assessed by serial angiography.²⁰ This may have been an effect on inhibiting thrombotic occlusion of stenotic vessels rather than retarding stenosis progression. The Physicians Health Study, a primary prevention study, found that aspirin 325 mg qod day decreased the need for peripheral arterial reconstructive surgery²¹; however, no difference was noted between the aspirin and placebo groups in the development of intermittent claudication.

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DOI: 10.1378/chest.08-0686

Other chapters in these guidelines describe the compelling evidence for aspirin in patients with coronary artery disease and stroke. This applies to many patients with chronic arterial insufficiency who also have clinically manifest coronary or cerebrovascular disease. Most patients with PAD who do not have clinically manifest disease have occult coronary or cerebrovascular disease.

1.1.2 Thienopyridines: Ticlopidine and Clopidogrel

One metaanalysis has demonstrated that patients with intermittent claudication treated with ticlopidine had a significant reduction in fatal and nonfatal cardiovascular events in comparison with patients treated with placebo.²² However, ticlopidine is associated with a substantial risk of leukopenia and thrombocytopenia, requiring close hematological monitoring. Because of these side effects, clopidogrel has replaced ticlopidine as the thienopyridine of choice.

In a large multicenter, RCT of 19,185 patients (CAPRIE), investigators compared the relative efficacy of clopidogrel vs aspirin in reducing the risk of a composite end point of ischemic stroke, MI, or vascular death.²³ The study population comprised patients with recent ischemic stroke, recent MI, or PAD. The overall incidence of composite end points was lower in the group treated with clopidogrel (5.32% per year) than with aspirin (5.83%; $p = 0.043$). A *post hoc* subgroup analysis suggested a larger benefit of clopidogrel over aspirin in patients who were eligible for the study because of symptomatic PAD than those enrolled because of their manifestations of cardiac or cerebrovascular disease. However, the significance of such subgroup analyses are questionable.

Other trials have compared combinations of aspirin and clopidogrel to single agents. The MATCH trial compared clopidogrel plus placebo to clopidogrel plus aspirin in patients with symptomatic cerebrovascular disease and additional vascular risk factors (including PAD).²⁴ Composite event rates at 18 months for the 776 patients with PAD showed a nonsignificant reduction in risk with combined therapy (19.1% for clopidogrel + aspirin, and 24% for clopidogrel alone). Nor were the differences significant for the overall group (> 7,000 patients). Combined therapy with clopidogrel + aspirin carried a higher risk of major hemorrhagic complications.

The CHARISMA trial studied primary and secondary prevention in patients with high atherosclerotic risks, of whom 23% had PAD.²⁵ The composite ischemic event rate was similar in those treated with aspirin alone (7.3%), vs aspirin plus clopidogrel (6.8%). The results for patients with PAD were not

analyzed separately. A reanalysis restricted to the patients in the CHARISMA trial who had PAD, prior myocardial infarction (MI), or stroke revealed a composite ischemic event rate of 7.3% for clopidogrel plus aspirin, compared to 8.8% for aspirin alone.²⁶ This difference was statistically significant. Moderate bleeding complications were more common with dual therapy.

In summary, long-term combined antiplatelet therapy with clopidogrel and aspirin likely carries a higher risk of bleeding, and results have failed to convincingly demonstrate superiority of dual therapy for reducing major vascular events in the long term. Likewise, monotherapy with clopidogrel may be marginally superior to aspirin, although the confidence interval in CAPRIE bordered on no effect. The cost of monotherapy with clopidogrel (especially for lifetime therapy) is much higher than that of aspirin.

1.1.3 Further Discussion of Clopidogrel vs Aspirin Including Resource Use

The general topic of long-term clopidogrel use for secondary prevention in patients with atherosclerotic vascular disease, and its economic implications, have been reviewed in the chapter on chronic CAD. For the purpose of this chapter, we must ask whether the case for clopidogrel in CAD must be modified importantly when considering the subset of patients with atherosclerotic peripheral arterial disease. While patients with peripheral arterial disease are represented in all the major trials of clopidogrel vs aspirin alone, only the CAPRIE Trial has presented a detailed subgroup analysis for these patients.²⁷ In CAPRIE, the peripheral arterial disease subgroup demonstrated the largest relative benefit from clopidogrel therapy seen in the trial, a 24% relative reduction in vascular death, myocardial infarction or stroke ($p = .003$). In addition, the trial found statistical evidence that this treatment benefit was greater in PAD patients than that for the subsets with previous MI and previous strokes.

Secondary analyses of patients in the PAD and stroke subgroups who also had a prior MI suggested that clopidogrel reduced the primary event rate in those with prior MI by 23%, providing at least some support for the contention that the heterogeneity in treatment benefits seen in CAPRIE was due to the play of chance rather than true differential treatment effects. The subset of patients with previous MI derived from the PAD and stroke subgroups had an annual event rate on aspirin of 10.7% while the originally defined PAD

and MI subgroups had annual event rates on aspirin of about 4.8%. Thus, treatment benefit does not seem to be a simple function of underlying risk of disease-related complications.

Further, although the factors that lead one patient to become most symptomatic with disease in the peripheral arterial tree rather than the carotid or coronary arteries are not yet understood, the corresponding clinical phenotypes do not appear sufficiently distinct to serve as guides for the differential use of preventive antiplatelet therapy. Thus, from an economic perspective, the benefits and economic attractiveness attached to secondary prevention with intermediate-term clopidogrel therapy in chronic CAD would seem to apply fully to the subset of patients with PAD (*ie*, for 8 to 12 months). However, the applicability of intermediate term clopidogrel therapy to PAD poses a further challenge, because unlike MI and stroke, the onset of PAD is not usually so temporally distinct. When the available empirical data are incorporated into cost-effectiveness models, along with reasonable extrapolations, results suggest that very long-term or lifetime prevention with clopidogrel therapy in PAD does not have sufficient value to support a case for cost-effectiveness.^{28,29}

1.1.4 Picotamide

Picotamide, an anti-platelet agent that inhibits thromboxane A₂ synthase and antagonizes thromboxane A₂ receptors, has been evaluated in a blinded, RCT in 2,000 patients with PAD.³⁰ Treatment with picotamide significantly reduced the overall incidence of major and minor cardiovascular events. In a blinded, placebo-controlled RCT, patients treated with picotamide showed no progression of carotid atherosclerosis (as measured by B-mode ultrasound) compared with placebo-treated control subjects.³¹ These studies led to a head-to-head comparison between aspirin (320 mg/d) and picotamide (600 mg bid) conducted by the DAVID trial, focusing on the subgroup of type II diabetics with PAD.³² This multicenter, randomized blinded trial studied 1209 adults for 24 months. The cumulative 2-year overall mortality was significantly lower among patients treated with picotamide (3.0%) than in those with aspirin (5.5%). The risk ratio for picotamide vs aspirin was 0.55 (95% confidence interval [CI]: 0.31–0.98%). A secondary, combined end point of mortality and major cardiovascular morbidity was not significantly different between the treatment groups (7.1% of picotamide patients vs 8.7% of aspirin-treated patients). The incidence of hemorrhagic complications was no different between picotamide and aspirin, although GI disturbances

were more common with aspirin. Picotamide is approved for use in some European countries.

Recommendations

1.1.1.1. In PAD patients with clinically manifest coronary or cerebrovascular disease, we recommend lifelong antiplatelet therapy in comparison to no antiplatelet therapy (Grade 1A).

1.1.1.2. In those without clinically manifest coronary or cerebrovascular disease, we suggest aspirin (75–100 mg/d) over clopidogrel (Grade 2B). In patients who are aspirin intolerant, we recommend clopidogrel over ticlopidine (Grade 1B).

Values and preferences: This recommendation places a relatively high value on avoiding large expenditures to achieve uncertain, small reductions in vascular events.

1.1.2 Anticoagulants for PAD

A Cochrane review assessed the effects of anticoagulant drugs on long-term vascular mortality and cardiovascular events in patients with PAD.³³ Thirteen trials were initially considered eligible for inclusion in the review (including unfractionated heparin [UFH], low-molecular-weight heparin [LMWH] and vitamin K antagonists [VKAs]). Only three studies (two evaluating VKA, one evaluating UFH) met the high-quality methodologic eligibility criteria and were included in the primary analysis, while four other studies were included in the sensitivity analysis. No study reported a significant effect on overall mortality or cardiovascular events, and the pooled odds ratios were not significant for these outcomes. Major and minor bleeding events were significantly more frequent in patients treated with VKA compared to control, with a nonsignificant increase in fatal bleeding events. Thus, no benefit has been established for UFH, LMWHs or VKA to reduce overall vascular mortality or cardiovascular ischemic events in patients with PAD. An increased risk of major bleeding events has been observed especially with VKA.

Recommendation

1.1.2. In patients with PAD and intermittent claudication, we recommend against the use of anticoagulants to prevent vascular mortality or cardiovascular events (Grade 1A).

1.1.3 Antithrombotic Therapy for Intermittent Claudication

It is most important to note that intermittent claudication, *per se*, carries a relatively benign prognosis for the legs, and is quite responsive to exercise

therapy. Systematic reviews and metaanalyses of randomized trials of exercise therapy in patients with claudication suggest that exercise improves maximal walking distance by 150%.³⁴ Supervised exercise programs are more effective than nonsupervised regimens.³⁵ Accordingly, an exercise program (and treatment of modifiable risk factors) should be considered the first line therapy for intermittent claudication. Drug therapy to treat the symptoms of claudication should be considered as a second line of treatment. Tables 1, 2 summarize the data on claudication discussed in the following sections. See the online data supplement containing additional tables for this chapter at <http://www.chestjournal.org>.

1.1.4 Antiplatelet Therapy for Intermittent Claudication

A study of 54 patients with intermittent claudication found the combination of aspirin and dipyridamole to increase the pain-free walking distance and resting limb blood flow.³⁶ An RCT of 296 patients with intermittent claudication found an improved coagulation profile and ankle/brachial index with therapy but did not report if walking distance improved with combined therapy.³⁷ Ticlopidine has also shown a modest beneficial effect for relieving symptoms, increasing walking distance and improving lower extremity ankle pressure indexes in patients with intermittent claudication.^{38,39} In a multicenter, placebo-controlled RCT, ticlopidine (250 mg/d) resulted in fewer vascular surgery procedures (relative risk = 0.49; $p < 0.001$) among patients with intermittent claudication.⁴⁰ Overall, there is limited data supporting classical antiplatelet drugs for the treatment of intermittent claudication, and their value has been eclipsed by drugs specifically aimed at treating the symptoms of claudication.

Cilostazol: Cilostazol is a type III phosphodiesterase inhibitor that suppresses platelet aggregation and is a direct arterial vasodilator. Its mechanism of action as a treatment for claudication is not fully understood. Cilostazol has weak platelet inhibitory effects and there are no current data to support its use as an antiplatelet agent, although studies are currently underway. Antiplatelet therapy with aspirin or clopidogrel should be continued in patients taking cilostazol. Many clinical trials have evaluated the efficacy of cilostazol as a therapeutic agent for intermittent claudication, and two metaanalyses has also been published.^{41,42} Table 1 summarizes the clinical trials comparing cilostazol vs placebo, or pentoxifylline.

In treatment programs ranging from 12 to 24 weeks, cilostazol (100 mg bid) increases maximal

walking distance by 50%, and pain-free walking distance by 67%. In contrast, maximal walking distance is increased significantly less by pentoxifylline (38%) or placebo (21%) treatment. Age, sex, and the presence of diabetes do not appear to influence the clinical responses to the drug. Improvements can be observed within 4 weeks of therapy, but are not sustained after withdrawal of the drug.⁴¹

Cilostazol also improves quality of life scores for physical well-being. A direct relationship has been established between performance on a treadmill test, and a patient's subjective assessment of their walking ability, physical capacity, functional status and pain in their activities of daily living.⁴³⁻⁴⁶ Three of the six trials of cilostazol vs placebo conducted objective quality of life and subjective functional status assessments, using well-validated quality of life (QOL) tools: the Short Form-36 (SF-36), the Walking Impairment Questionnaire (WIQ), and the Claudication Outcome Measures (COM). These QOL outcomes were homogeneous, and consistent with the treadmill results in all studies. A metaanalysis of the effects of cilostazol on QOL and walking ability confirmed its positive effects on both.⁴³

Cilostazol is more effective than the other leading agent for claudication, pentoxifylline, as illustrated in a study of 698 patients randomized to pentoxifylline (400 mg tid), cilostazol (100 mg bid), or placebo for 24 weeks.⁴⁷ In comparison to pentoxifylline, cilostazol produced a significant increase in the walking distance to onset of claudication (218 m for cilostazol vs 202 m for pentoxifylline, $p = 0.0001$) and absolute claudication distance (ACD) (350 m for cilostazol vs 308 m for pentoxifylline, $p = 0.0005$). In addition, there were fewer patients who had no change or deterioration in walking distance (23% for cilostazol vs 34% with pentoxifylline).

Cilostazol is generally well tolerated, although contraindicated in patients with congestive heart failure. Side effects of headache, bowel complaints, and palpitations are seen more frequently with cilostazol treatment, compared with placebo. Cilostazol is appropriate therapy for patients with moderate to severe disabling claudication who are not candidates for revascularization. However, considering the high level of effectiveness of an exercise program, and the more modest effects of cilostazol on walking distance, its use in patients with less disabling intermittent claudication is questionable.

Pentoxifylline: Pentoxifylline is a weak antithrombotic agent; its putative mechanisms of action include an increase in RBC deformity, and decreases in fibrinogen concentration, platelet adhesiveness, and whole-blood viscosity.⁴⁸⁻⁵⁰ One metaanalysis of a total of 612 patients suggests that pentoxifylline

Table 1—RCTs of Cilostazol or Pentoxifylline in Patients With Intermittent Claudication: Clinical Description and Results (Section 1.1.3)*

Study/yr	Interventions	Patients Analyzed, No./ Total	Length of Follow-up	Mean Measures	Clinical Outcome Measures and % Change From Baseline	QOL/Functional Status (Other Comments)
Cilostazol vs placebo or conventional care						
Beebe et al ^{196/1999}	Cilostazol 100 mg bid Cilostazol 50 mg bid Placebo	Cilostazol 100 mg bid: 138/175 Cilostazol 50 mg bid: 139/171 Placebo: 141/170	24 wk	ACD: Cilostazol 100 mg bid: 258.8 m Cilostazol 50 mg bid: 198.8 m Placebo: 174.6 m ICD: Cilostazol 100 mg bid: 137.9 m Cilostazol 50 mg bid: 115.1 m Placebo: 95.5 m	ACD: Cilostazol 100 mg bid: + 51% Cilostazol 50 mg bid: + 38% Placebo: + 20% ICD: Cilostazol 100 mg bid: + 59% Cilostazol 50 mg bid: + 48% Placebo: + 20%	SF-36 physical function Cilostazol 50 mg bid/100 > placebo p = 0.02 SF-36 bodily pain Cilostazol 50 mg bid/100 > placebo p = 0.002 WQ: CLZ > placebo p = 0.01 COM walking pain and walking pain in activities CLZ > placebo p = 0.001
Dawson et al ^{197/1998}	Cilostazol 100 mg bid Placebo	Cilostazol 100 mg bid: 44/54 Placebo: 22/27	12 wk	ICD (SD): Cilostazol 100 mg bid: 112.5 m (13.8) Placebo: 84.6 m (13.7); ACD (SD): Cilostazol 100 mg bid: 231.7 m (36.9) Placebo: 152.1 m (23.9) ACD (SD): Cilostazol 100 mg bid: 350 m (209) Placebo: 300 m (180) ICD: Cilostazol 100 mg bid: 218 m (149) Placebo: 180 m (115) ACD (SEM): Cilostazol 100 mg bid: 335 m (24) Placebo: 304 m (23)	ICD: Cilostazol 100 mg bid: + 31.7% Placebo: - 2.5% ACD: Cilostazol 100 mg bid: + 30.5% Placebo: - 9.3% ACD: Cilostazol 100 mg bid: + 44% Placebo: + 28% ICD: Cilostazol 100 mg bid: + 76% Placebo: + 46% ACD: Cilostazol 100 mg bid: + 35.5% Placebo: + 24.3% ACD (SD): Cilostazol 100 mg bid: + 96.4% (57) Placebo: + 31.4% (12.9)	
Dawson et al ^{198/2003}	Cilostazol 100 mg bid Placebo	Cilostazol 100 mg bid: 166/227 Placebo: 201/239	24 wk			
Elam et al ^{199/1998}	Cilostazol 100 mg bid Placebo	Cilostazol 100 mg bid: 82/95 Placebo: 88/94	12 wk			
Money et al ^{200/1998}	Cilostazol 100 mg bid Placebo	Cilostazol 100 mg bid: 104/119 Placebo: 108/120	16 wk			SF-36 physical component CLZ > placebo p = 0.006 SF-36 physical function CLZ > placebo p = 0.002 WQ: CLZ > placebo p = 0.03 SF-36 physical function Cilostazol 100 mg bid > placebo p = 0.048
Strandness et al ^{201/2002}	Cilostazol 100 mg bid Cilostazol 50 mg bid Placebo	Cilostazol 100 mg bid: 124/133 Cilostazol 50 mg bid: 128/132 Placebo: 125/128	24 wk	Cilostazol 100 mg bid: 195.6 m Cilostazol 50 mg bid: 166.5 m Placebo: 141.2 m	ACD: Cilostazol 100 mg bid: + 63.82% Cilostazol 50 mg bid: + 33.5% Placebo: + 20.8%	
Cilostazol vs pentoxifylline						
Dawson et al ^{196/2000}	Cilostazol 100 mg bid Pentoxifylline 400 mg tid	Cilostazol 100 mg bid: 166/227 Pentoxifylline 400 mg tid: 172/232	24 wk	ACD (SD): Cilostazol 100 mg bid: 350 m (209) Pentoxifylline 400 mg tid: 308 m (183) ICD (SD): Cilostazol 100 mg bid: 218 m (149) Pentoxifylline 400 mg tid: 202 m (139)	ACD: Cilostazol 100 mg bid: + 44% Pentoxifylline 400 mg tid: + 26% ICD: Cilostazol 100 mg bid: + 76% Pentoxifylline 400 mg tid: + 58%	

Table 1—Continued

Study/yr	Interventions	Patients Analyzed, No./ Total	Length of Follow-up	Mean Measures	Clinical Outcome Measures and % Change From Baseline	QOL, Functional Status (Other Comments)
Pentoxifylline vs placebo or conventional care						
Belcaro et al ^{202/} 2002	Pentoxifylline 1,600 mg/d Placebo	Pentoxifylline 1,600 mg/d: 27/30 Placebo: 26/30	6 mo		TWD: Pentoxifylline 1,600 mg/d: +292% Placebo: +180% ICD: Pentoxifylline 200 mg tid: +208% Placebo: +52% ICD: Pentoxifylline 1,600 mg/d: +386% Placebo: 369% TWD: Pentoxifylline 1,600 mg/d: +329% Placebo: 183%	Diabetics
Bollinger and Frei ^{153/} 1977	Pentoxifylline 200 mg tid Placebo	Pentoxifylline 200 mg tid: 10/13 Placebo: 9/13	8 wk		ACD (SD): Pentoxifylline 400 mg tid: 308 m (183) Placebo: 300 m (180) ICD (SD): Pentoxifylline 400 mg tid: 202 m (139) Placebo: 180 m (115)	Also included substudy ¹⁰
Cesarone et al ^{203/} 2002	Pentoxifylline 1,600 mg/d Placebo	Pentoxifylline 1,600 mg/d: 88/100 Placebo: 90/100	40 wk		Placebo: +46% TWD: Pentoxifylline 1,800 mg/d +170% Placebo: +131% TWD: Pentoxifylline 600 mg tid: +404% Placebo: +280% PFWT: Placebo +149% Pentoxifylline 400 mg tid: +189% ICD: Pentoxifylline 400 mg tid: +60% Placebo: +3%	Long-distance claudicators (> 400 m)
Dawson et al ^{198/} 2000	Pentoxifylline 400 mg tid Placebo	Pentoxifylline 400 mg tid: 172/232 Placebo: 201/239	24 wk			
De Sanctis et al ^{204/} 2002	Pentoxifylline 1,800 mg/d Placebo	Pentoxifylline 1,800 mg/d: 75/98 Placebo 60/96	12 mo			
De Sanctis et al ^{205/} 2002	Pentoxifylline 600 mg tid Placebo	Pentoxifylline 600 mg tid: 56/60 Placebo 45/60	12 mo			
Dettori et al ^{60/} 1989	Pentoxifylline 400 mg tid Placebo	Placebo 30/37 Pentoxifylline 400 mg tid: 29/37	1 yr			
Di Perri and Guerrini ^{54/} 1983	Pentoxifylline 400 mg tid Placebo	Pentoxifylline 400 mg tid: 12/12 Placebo 12/12	8 wk/period			

Table 1—Continued

Study/yr	Interventions	Patients Analyzed, No./ Total	Length of Follow-up	Mean Measures	Clinical Outcome Measures and % Change From Baseline	QOL, Functional Status (Other Comments)
Callus et al ⁶¹ / 1985	Pentoxifylline 400 mg bid Placebo	Pentoxifylline 400 mg tid: 19/50 Placebo 19/50	7 wk/period		TWD: Period 1: Pentoxifylline 400 mg bid: + 33% Placebo: + 14% Period 2: Pentoxifylline 400 mg bid: + 14% Placebo: + 36% Claudication distance Period 1: Pentoxifylline 400 mg bid: + 155% Placebo + 126% Period 2: Pentoxifylline 400 mg bid: + 124% Placebo: + 172% ACD (SD): Pentoxifylline 400 mg tid: + 50% (9) Placebo: + 29% (8) ICD: Pentoxifylline 200 mg tid: + 45% Placebo: + 23% ACD: Pentoxifylline 200 mg tid: + 32% Placebo: + 20% ACD: Pentoxifylline + 27% Placebo: + 89% ACD: Pentoxifylline 400 mg tid: + 101% Placebo: + 9% ICD: Pentoxifylline 400 mg tid: + 124% Placebo: + 28%	Double-blind crossover design with 1 wk washout
Lindgarde et al ⁵⁷ /1989	Pentoxifylline 400 mg tid Placebo	Pentoxifylline 400 mg tid: 58/76 Placebo 51/74	24 wk			Outcomes also given for four subpopulations
Porter et al ⁵⁹ / 1982	Pentoxifylline 200 mg tid Placebo	Pentoxifylline 42/67 Placebo 40/61	24 wk			
Reilly et al ⁶³ / 1987	Pentoxifylline (no dosage given) Placebo	Pentoxifylline 15/16 Placebo 10/14	12 wk			All subjects, placebo 4 wk before trial; pentoxifylline last 4 wk of trial
Roekaerts and Deleers ⁵⁵ / 1984	Pentoxifylline 400 mg tid Placebo	Pentoxifylline 400 mg tid: 10/10 Placebo 10/10	6 mo/ period			Crossover RCT arm 1

Table 1—Continued

Study/yr	Interventions	Patients Analyzed, No./Total	Length of Follow-up	Mean Measures	Clinical Outcome Measures and % Change From Baseline	QOL, Functional Status (Other Comments)
Roekaerts and Deleers ^{55/} 1984	Parallel RCT Pentoxifylline 400 mg tid Placebo	Pentoxifylline 400 mg tid: 8/8 Placebo 8/8	9 mo		ACD: Pentoxifylline 400 mg tid: + 121% Placebo: - 15% ICD: Pentoxifylline 400 mg tid: + 138% Placebo: - 25% ICD: PXF + 46% when crossed → placebo: - 19% Placebo: + 4% when crossed → pentoxifylline 400 mg bid: + 32% TWD: Pentoxifylline 200 mg bid: + 126% Placebo: + 38% TWD: Pentoxifylline 300 mg IV infusion and 200 mg bid: + 76% Placebo: + 15%	Crossover RCT arm 2
Straño et al ^{56/} 1984	Pentoxifylline 400 mg bid Placebo	18/18	90 d/ period		ACD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening: + 51% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 44% ICD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening + 54% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 46% ACD: Pentoxifylline 400 mg tid: + 100% Aspirin + 50%	Crossover trial
Tonak et al ^{206/} 1977	Pentoxifylline 200 mg bid Placebo	Pentoxifylline 200 mg bid: 27/30 Placebo 28/30	14 d		ACD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening: + 51% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 44% ICD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening + 54% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 46% ACD: Pentoxifylline 400 mg tid: + 100% Aspirin + 50%	Ambulatory patients
Tonak et al ^{206/} 1977	Pentoxifylline 300 mg IV infusion and 200 mg bid Placebo	Pentoxifylline 27/30 Placebo 28/30	14 d		ACD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening: + 51% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 44% ICD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening + 54% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 46% ACD: Pentoxifylline 400 mg tid: + 100% Aspirin + 50%	Hospitalized patients
Pentoxifylline vs other						
Bieron et al ^{207/} 2005	Pentoxifylline 300 mg in IV solution morning and 400 mg po evening Bencyclane 200 mg in IV solution morning and 200 mg po evening	Pentoxifylline 300 mg in IV solution morning and 400 mg po evening: 18/18 Bencyclane 200 mg in IV solution morning and 200 mg po evening: 18/18	14 d		ACD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening: + 51% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 44% ICD: Pentoxifylline 300 mg in IV solution morning and 400 mg po evening + 54% Bencyclane 200 mg in IV solution morning and 200 mg po evening: + 46% ACD: Pentoxifylline 400 mg tid: + 100% Aspirin + 50%	Level of pain (improvement on scale 5-1): Pentoxifylline 400 mg tid: no change Aspirin 2/5 to 1/5
Ciocon et al ^{58/} 1997	Pentoxifylline 400 mg tid Aspirin 325 mg/d	Pentoxifylline 400 mg tid: 45/45 Aspirin 45/45	6 wk		ACD: Pentoxifylline 400 mg tid: + 100% Aspirin + 50%	Level of pain (improvement on scale 5-1): Pentoxifylline 400 mg tid: no change Aspirin 2/5 to 1/5

Table 1—Continued

Study/yr	Interventions	Patients Analyzed, No./ Total	Length of Follow-up	Mean Measures	Clinical Outcome Measures and % Change From Baseline	QOL, Functional Status (Other Comments)
Dettori et al ⁶⁰ / 1989	Pentoxifylline 400 mg tid Acenocoumarol 4 mg Pentoxifylline and acenocoumarol tid Placebo	Pentoxifylline 400 mg tid 29/37 Acenocoumarol 4 mg 30/36 Pentoxifylline and acenocoumarol tid 29/36 Placebo: 30/37	1 yr		PFWT: Pentoxifylline 400 mg tid: + 189% Acenocoumarol 4 mg + 236% Pentoxifylline and acenocoumarol tid: + 239% Placebo: + 149%	Distance not measured
Strano et al ²⁰⁸ / 2002	Pentoxifylline 400 mg tid Propionyl-L-carnitine 500 mg tid	Pentoxifylline 400 mg tid: 34/60 Propionyl-L-carnitine 500 mg tid: 34/54	12 mo		ACD: Pentoxifylline 400 mg tid: + 54% Propionyl-L-carnitine 500 mg tid + 123% ICD: Pentoxifylline 400 mg tid: + 67% Propionyl-L-carnitine 500 mg tid: + 174%	

*ICD = initial claudication distance; TWD = total walking distance; PXF = pentoxifylline; CLZ = cilostazol; PFWT = pain-free walking time. The methodological quality description portion of the table can be found in the online version of this article as a data supplement.

improves pain-free walking distance by 29 m compared with placebo,⁵¹ although the improvement was approximately 50% in the placebo group, and use of pentoxifylline improved absolute walking distance by an additional 30%. Another metaanalysis came to similar conclusions.⁵²

A number of clinical trials of pentoxifylline have shown conflicting results. Some concluded that pentoxifylline was significantly more effective than placebo in improving treadmill-walking distance^{53–58} but others could not demonstrate benefit.^{59–64} In many trials, patients treated with placebo also demonstrated significant improvement. Thus, the actual improvement in walking distance attributable to pentoxifylline is often unpredictable and may not be clinically important compared with the effects of placebo.⁶⁵ In summary, the evidence for a beneficial effect of pentoxifylline is not strong enough to suggest an important role in the treatment of patients with PAD.^{66,67}

Recommendation

1.1.4. For patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, we recommend cilostazol (Grade 1A). We suggest that clinicians not use cilostazol in those with less-disabling claudication (Grade 2A). We recommend against the use of pentoxifylline (Grade 2B).

Values and preferences: Because of the cost of cilostazol therapy, and the safety and efficacy of an exercise program, we recommend cilostazol treatment be reserved for patients with moderate-to-severe claudication who have tried and failed an exercise program, and are not candidates for vascular surgical or endovascular procedures.

1.1.5 Anticoagulants for Intermittent Claudication

A Cochrane systematic review found no benefits from anticoagulant drugs in the treatment of intermittent claudication.³³ The agents studied included UFH, LMWH, and VKAs. End points were walking capacity (pain-free walking distance or absolute walking distance), ankle/brachial pressure index, progression to surgery, amputation-free survival, and side effects. The trials did not address QOL. Thirteen trials were initially considered eligible for inclusion in the review. Only three studies (two evaluating VKA, one evaluating UFH) met the high-quality methodologic inclusion criteria and were included in the primary analysis, while four other studies were included in the sensitivity analysis. No significant difference was observed between UFH treatment

and control groups for pain-free walking distance or maximum walking distance at the end of treatment. The review found no data to indicate that LMWHs benefit walking distance. Major and minor bleeding events were significantly more frequent in patients treated with VKA compared to control, with a non-significant increase in fatal bleeding events. No major bleeding events were reported in the study evaluating UFH, while a nonsignificant increase in minor bleeding events was reported. An increased risk of major bleeding events has been observed especially with VKA. In conclusion, no benefit of UFH, LMWHs, or VKA has been established for intermittent claudication.

Recommendation

1.1.5. For patients with intermittent claudication, we recommend against the use of anticoagulants (Grade 1A).

1.1.6 Prostaglandins for Critical Limb Ischemia and Claudication

Investigators have administered prostaglandins to patients with advanced chronic arterial insufficiency in hopes of relieving rest pain and healing ischemic ulcers. These prostaglandins (prostaglandin E₁, prostaglandin I₂, and their derivatives) have potent antiplatelet and vasodilatory effects, and are administered IV or intraarterially. In a study of 80 patients with intermittent claudication, IV administration of a prostaglandin E₁ produced a dose related improvement in walking distance and QOL at 4 weeks and 8 weeks.⁶⁸ In an older but larger randomized, blinded, multicenter trial of patients with one to three ischemic ulcers not healing for 3 weeks with standard care who were randomized to receive either prostaglandin E₁ or a placebo for 72 h through a central venous catheter, prostaglandin E₁ was found to be ineffective.⁶⁹ In a small, randomized open study, prostaglandin E₁ administered IV and combined with an intensive exercise regimen produced dramatic and sustained improvement in symptom-free walking distance in comparison with exercise alone or exercise combined with IV-administered pentoxifylline.⁷⁰ The largest data set comes from a multicenter, randomized clinical trial⁷¹ in which 1,560 patients with chronic critical ischemia of the leg were randomly assigned to receive either a daily IV infusion of prostaglandin E₁ or nothing (open-label study) during their hospital stay. At discharge, there was a greater reduction in composite outcome events in the PGE₁ group than in the control subjects (63.9% vs 73.6%; relative risk, 0.87; $p < 0.001$), but this difference was not statistically significant at 6 months (52.6% vs 57.5%; relative risk, 0.92;

$p = 0.074$). AS-013, a prostaglandin E₁ prodrug, was evaluated in a small randomized trial of 80 patients with claudication and was associated with an increase of 35m in maximal walking distance after 8 weeks of treatment, compared with a slight decrease in placebo-treated control subjects.⁷² This difference was statistically significant ($p < 0.01$), although the clinical significance of the increase was marginal and the investigators did not measure quality of life directly.

A blinded trial that contained a high proportion of diabetics showed no beneficial effect of IV prostaglandin I₂ on ulcer healing or rest pain.⁷³ However, selective intraarterial prostaglandin I₂ was found to relieve rest pain and promote healing of ulcers to a significantly greater degree than did placebo treatment in 30 nondiabetic patients, half of whom had thromboangiitis obliterans (Buerger disease).⁷⁴ In another blinded trial, prostaglandin I₂ given IV to nondiabetic patients with severe arterial insufficiency produced significantly greater relief (lasting up to 1 month) of rest pain than did placebo,⁷⁵ but there was no correlation with changes in ankle-to-brachial pressure index, or ulcer healing.

Beraprost, an orally active prostaglandin I₂ analog, was evaluated in the BERCI-2 trial of 549 patients with a pain-free walking distance of 50 to 300 m.⁷⁶ After six months, more patients taking beraprost (40 μg tid) compared to placebo had an increase in walking distance on a treadmill (44% vs 33%), pain free walking distances (82% vs 53%), and maximum walking distances (60% vs 35%). These modest improvements have not been borne out by a subsequent blinded randomized trial of 897 patients, in which beraprost treatment conferred no improvements in maximal walking distance.⁷⁷ In neither trial did beraprost significantly reduce the composite end point of cardiac death, MI, coronary revascularization, stroke, transient ischemic attack (TIA), or critical leg ischemia requiring intervention.

Recommendation

1.1.6. For patients with limb ischemia, we suggest clinicians do not use prostaglandins (Grade 2B).

1.1.7 Other Agents To Treat Intermittent Claudication

Investigators have tested other agents with putative antithrombotic activity in RCTs and found no clinically significant effects on intermittent claudication. These include the antiserotonin agent ketanserin,⁷⁸ fish oil supplementation,⁷⁹ and naftidrofuryl.^{80,81} Other ineffective drugs for intermittent claudication include nifedipine and l-carnitine. "Hemodilution therapy" reduces the plasma viscosity by

the removal of blood and replacing it with a colloidal solution such as hydroxyethyl starch or a low-molecular-weight dextran one to two times weekly for several weeks. Two randomized trials showed small improvements in pain-free walking distance with hemodilution.^{82,83}

2.0 ACUTE LIMB ISCHEMIA

2.1 Anticoagulation for Acute Limb Ischemia

The causes of nontraumatic acute arterial occlusion in the limbs are embolic or thrombotic. The large majority of emboli arise from the heart in patients with valvular disease and/or atrial fibrillation, with prosthetic valves, or with mural thrombi in an infarcted or dilated left ventricle. Noncardiac sources of embolism include arterial aneurysms, ulcerated atherosclerotic plaque, recent (endo)vascular procedures, paradoxical emboli from venous thrombi, and rarely arteritis or vascular trauma. Approximately two thirds of noncerebral emboli enter vessels of the lower extremity and half of these obstruct the iliofemoral segment while the remainder involve the popliteal and tibial vessels. The upper extremity and renal plus visceral vessels each receive approximately 15% of emboli.^{84,85}

Thrombotic occlusions of arteries are usually associated with advanced atherosclerosis, and the limb has typically developed a collateral blood supply. For this reason, the final occlusion of a stenotic vessel may not be a dramatic event and is sometimes silent; it is not an emergency in many patients. The upper extremity better tolerates arterial occlusion because of rich collateral blood supply: gangrene or ischemic rest pain is rare in the absence of distal embolization. Hypovolemia, hyperviscosity, and hypercoagulability as observed in shock, thrombocytosis, polycythemia, and malignant disorders predispose to thrombotic arterial occlusion. Arterial thrombosis most frequently involves the lower extremities. Therapeutic management depends on whether the occlusion is caused by embolism in a healthy artery vs thromboembolism in an atheromatous artery. Prompt embolectomy through surgical intervention is the usual technique to remove emboli from healthy arteries. The introduction of the Fogarty balloon catheter > 40 years ago dramatically decreased the mortality and the amputation rate from arterial embolism. Percutaneous thromboembolectomy with the aid of an aspiration catheter or of a thrombectomy device is a recent alternative. Literature on either of these new techniques is descriptive.^{86,87} To our knowledge, no randomized comparison between the different options is available.

Patients presenting with acute limb ischemia second-

ary to thromboembolic arterial occlusion usually receive prompt anticoagulation with therapeutic dosages of heparin in order to prevent clot propagation and to obviate further embolism. The logic of this common clinical practice is not questioned, even though no formal studies have established unequivocally a beneficial role of any antithrombotic agent in patients with acute embolic occlusion. The expected adverse effect of perioperative anticoagulant therapy is an increased risk of wound complications, particularly hematomas. The major role for continued anticoagulant therapy (heparin followed by oral anticoagulants) after embolization is to prevent embolic recurrence if the source of embolism cannot be eradicated or corrected.

Recommendation

2.1. In patients with acute arterial emboli or thrombosis, we recommend immediate systemic anticoagulation with UFH, over no anticoagulation (Grade 1C). In patients undergoing embolectomy we suggest following systemic anticoagulation with UFH with long-term anticoagulation with VKA (Grade 2C).

2.2 Thrombolysis for Acute Limb Ischemia

Initial intervention with thrombolysis, with the aim to eliminate all thrombotic and embolic material and restore perfusion, is a potential alternative to surgical revascularization in acute limb ischemia of thromboembolic origin. Systemic thrombolysis with IV administration of a thrombolytic agent as used in the 1960s and 1970s has been completely abandoned and replaced by catheter-directed thrombolysis. With this technique, a catheter is positioned intra-arterially and advanced into the thrombus for local delivery of the thrombolytic agent. Initially, streptokinase was the most widely used agent, but later it was superseded in clinical use by urokinase and recombinant tissue-type plasminogen activator (rt-PA [alteplase]). Clinicians can use several infusion methods and dosages schemes vary considerably: no infusion regimen has proved superior.^{88,89} Investigators studied reteplase and tenecteplase, two mutants of alteplase: thrombus dissolution rates and bleeding rates appear comparable to published data with other thrombolytic agents but a direct comparison is not available.⁹⁰⁻⁹³ Other new agents tested or being tested but (not yet) in clinical use are staphylokinase, recombinant pro-urokinase and altimeprase.⁹⁴⁻⁹⁶ A few small trials have studied the addition of the platelet glycoprotein IIb-IIIa antagonists abciximab or eptifibatid as adjuvant therapy to thrombolysis with the hope of improving lytic efficacy and clinical outcome.⁹⁷⁻¹⁰⁰ The combination is feasible but the potential benefits need further investigation.

A few randomized studies compared thrombolytic agents directly. An open trial compared intraarterial streptokinase to intraarterial and IV rt-PA in 60 patients with recent onset or deterioration of limb ischemia: initial angiographic success was superior with intraarterial rt-PA (100%) than with intraarterial streptokinase (80%; $p < 0.04$) or IV rt-PA (45% $p < 0.01$), the 30-day limb salvage rates being 80%, 60%, and 45%, respectively.¹⁰¹ Another randomized trial enrolled 32 patients and showed significantly faster lysis with rt-PA than with urokinase, but the 24-h lysis rate and the 30-day clinical success rate were similar.¹⁰² The Surgery vs Thrombolysis for Ischemia of the Lower Extremity (STILE) study, an RCT comparing rt-PA and urokinase, showed similar efficacy and safety for both agents.¹⁰³ A German study randomized 120 patients with thrombotic infrainguinal arterial occlusion to treatment with urokinase or rt-PA and noted a slight improvement in successful lysis in all segments treated with rt-PA ($p < 0.05$), but local hematomas were more common.¹⁰⁴ The PURPOSE trial compared three doses of recombinant pro-urokinase to tissue culture urokinase with complete lysis as a primary end point: the highest lysis rate was obtained with the highest dose tested (8 mg/h for 8 h, then 0.5 mg/h), at the expense of a slightly increased frequency of bleeding and decrement in fibrinogen level.⁹⁵ In assessing all of these data, there is at present no convincing evidence of superiority of any agent for catheter-directed thrombolysis in terms of efficacy and safety.

Although the extensive literature on catheter-directed thrombolysis is largely descriptive, five prospective randomized studies compared this treatment method to surgical intervention. Two metaanalyses conclude that there is a similar mortality and amputation rate for thrombolysis and surgery; thrombolysis reduces the need for open major surgical procedures but causes more bleeding and distal embolization.^{105,106}

A first trial compared surgical thrombectomy to an intraarterial continuous infusion of alteplase in 20 patients only with acute arterial occlusion and severe leg ischemia, too small a number to reach a meaningful conclusion.¹⁰⁷ Ouriel et al¹⁰⁸ compared initial thrombolysis complemented with percutaneous angioplasty or/and surgery vs immediate surgery in 114 patients with limb-threatening ischemia due to native artery or graft occlusion of < 7 days duration. Thrombolysis dissolved the occluding thrombus in 70% of the patients. Limb salvage rate was similar in the two groups (82% at 1 year), but cumulative survival was significantly improved in patients randomized to thrombolysis due to fewer cardiopulmonary complications in hospital (84% vs 58% at 1 year, $p = 0.01$).

The STILE trial randomized 393 patients with nonembolic native artery or bypass graft occlusion in the lower limbs within the past 6 months to either optimal surgical procedure or intraarterial catheter-directed thrombolysis with rt-PA or urokinase.¹⁰³ The primary end point was a composite outcome of death, major amputation, ongoing or recurrent ischemia, and major morbidity. At 1 month, the primary end point was reached for 36.1% of surgical patients and 61.7% of thrombolysis patients ($p < 0.0001$). This difference was primarily due to ongoing/recurrent ischemia (25.7% vs 54.0%; $p < 0.0001$); lysis was unsuccessful in 28% of the patients assigned to thrombolysis because of failure of proper catheter placement, an inexplicably high rate. However, in a secondary analysis that stratified patients by the duration of their preprocedure ischemia, thrombolysis resulted in improved amputation-free survival at 6 months and shorter hospital stay in patients with acutely ischemic limbs (< 14 days), whereas surgical revascularization was more effective for more chronic ischemia (> 14 days).¹⁰³

Two additional publications analyzed the STILE trial on an intention-to-treat basis for the 30 days, 6 months and 1-year results, segregating patients with native artery from those with graft occlusion.^{109,110} Overall, the composite clinical outcome was in favor of surgery for both groups. In patients with native vessel occlusion, those with recent ischemia (< 14 days) had a similar 1-year death/amputation rate whether treated with surgery or with thrombolysis. In those with graft occlusion, limb loss at 1 year was significantly lower in patients with ischemia for < 14 days if treated with thrombolysis.¹¹⁰

The TOPAS investigators compared recombinant urokinase vs surgery in acute arterial occlusion (≤ 14 days).^{111,112} In a first dose-ranging trial they evaluated the safety and efficacy of three doses of recombinant urokinase in comparison with surgery in 213 patients.¹¹¹ The 4000 IU/min dosage appeared the most appropriate thrombolytic regimen (compared with 2,000 and 6,000 IU/min) for the first 4 h because it maximized lytic efficacy against the bleeding risk. They then tested this optimal dosage regimen (4,000 IU/min for the initial 4 h followed by 2,000 IU/min for up to 48 h) in a large multicenter trial enrolling 544 patients.¹¹² Amputation-free survival rates in the urokinase group were 71.8% at 6 months and 65.0% at 1 year, as compared with 74.8% and 69.9% in the surgery group; these differences were not significant. Thrombolysis reduced the need for open surgical procedures (315 vs 551 at 6 months) without increased risk of amputation or death.

Overall, the randomized trials provide no clear-cut answer to the dilemma of the preferred treatment

modality (thrombolysis or surgical intervention). The patient populations were heterogeneous, and the trials addressed complicated end points. The risk of intracranial bleeding remains a major risk for thrombolytic treatment in acute limb ischemia: in three American prospective randomized the intracranial bleeding rate with thrombolysis was 1.2% (STILE), 2.1% (TOPAS-I), and 1.6% (TOPAS-II).^{103,111,112}

For native artery occlusion of < 14 days duration, a Working Party proposed, a management strategy incorporating thrombolysis followed by correction of the causative lesion.⁸⁸ They recommended immediate surgical revascularization if thrombolysis would lead to an unacceptable delay in effective reperfusion. Recommendations included primary amputation in patients with irreversible ischemia. For occluded bypass grafts, the therapeutic options are either surgical thrombectomy with graft revision, catheter directed thrombolysis, or surgical insertion of a new bypass graft. Factors to consider in therapeutic decision making are the age and nature of the graft, the duration and degree of ischemia and the availability of vein for a new distal bypass. In patients with a recent occlusion of a well-established graft, the Working Party proposed thrombolytic therapy as a primary treatment modality. Thrombolysis may eventually clear the thrombosed outflow vessels as well. However, the patency rate 1 year after successful lysis of thrombosed grafts is low ($\pm 20\%$), and the question is whether the ultimate yield justifies the labor-intensive and expensive lytic procedure.¹¹³

Recommendation

2.2. In patients with short-term (< 14 days) thrombotic or embolic disease, we suggest intraarterial thrombolytic therapy (Grade 2B) provided patients are at low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization by this method.

Values and preferences: This recommendation places relatively little value on small reductions in the need for surgical intervention, and relatively high value on avoiding large expenditures and possible major hemorrhagic complications.

3.0 VASCULAR BYPASS GRAFTS

3.1 Intraoperative Anticoagulation During Vascular Reconstructions

IV UFH is traditionally given prior to clamping arteries and interrupting flow. The goals are to prevent stasis thrombosis in the often-diseased proximal and distal vessels, and to avoid the accumulation of thrombi at anastomoses and other sites of vascular

injury. Randomized trials of this therapy are probably not justified, and the primary question remains what should be the optimal intensity of anticoagulation during the procedure. Following the guidelines developed by cardiologists and interventional radiologists, some surgeons will monitor UFH dosage and responses using a point-of-care coagulation testing device such as the activated clotting time.¹¹⁴ In the absence of direct monitoring, a fairly intense level of anticoagulation is generally recommended during surgery because of the wide variability in patient's responses to UFH. A rational UFH regimen is to administer 100 to 150 U/kg IV before application of cross-clamps and to supplement this every 45 to 50 min with 50 U/kg until cross-clamps are removed and circulation is reestablished. The timing of the supplemental doses is based on the half-life of UFH (50 to 80 min).

Even in aortic surgery, where some surgeons do not consider UFH essential, anticoagulation may prevent remote thromboses. In a randomized clinical trial of 284 patients undergoing elective abdominal aortic aneurysm repair, there was no difference in the incidence of blood loss, transfusion requirement, or arterial thrombosis in patients receiving or not receiving UFH.¹¹⁵ However, those treated with UFH sustained fewer fatal MIs (1.4% vs 5.7%; $p < 0.05$) and nonfatal MIs (2.0% vs 8.5%; $p < 0.02$) than those who did not receive UFH.

During vascular surgery, tight control of intraoperative anticoagulation is favored, so low molecular weight heparins have not been widely studied because they have a longer duration of action, and are not completely reversed by protamine. One study of 849 patients from the Swedish Vascular Registry randomized patients to intraoperative anticoagulation with UFH (5,000 IU) or LMWH (enoxaparin 40 mg).¹¹⁶ Thirty-day patency rates were no different, and no cases of heparin-induced thrombocytopenia were encountered with either treatment. Median perioperative blood loss was 75 mL higher in the UFH group, which was deemed unimportant.

Even for UFH, reversal of anticoagulation with protamine after routine peripheral vascular surgery remains controversial. Protamine commonly causes adverse hemodynamic effects, and in diabetics receiving NPH insulin anaphylactic reactions may occur in 0.6–3.0% of patients.^{117–119} Moreover, reversal of UFH with protamine may not necessarily reduce postoperative bleeding. In a single-center randomized blinded study of 120 patients undergoing peripheral vascular surgery, protamine produced no difference in blood loss, bleeding complications, or transfusion requirement compared with those administered saline solution. One caveat is that the surgeons in this trial used a dose of UFH (90 U/kg)

that is lower than that suggested above, albeit with satisfactory results.¹²⁰ Also, rapid reversal of UFH anticoagulation with protamine may increase the risk of thrombosis, at least in carotid endarterectomy. In a small trial of randomized 64 patients who received protamine or no reversal, the amount of wound drainage was significantly less with protamine, while neck swelling was the same.¹²¹ Two patients receiving protamine suffered internal carotid artery thrombosis compared with none in the control group, although this difference was not statistically significant. UFH reversal with protamine sulfate after peripheral vascular surgery is subject to wide practice variations among surgeons; the desirability of reversal or nonreversal has not been established.

Recommendation

3.1. For patients undergoing major vascular reconstructive procedures, we recommend IV UFH, prior to the application of vascular cross-clamps (Grade 1A).

3.2 Lower-Extremity Vascular Reconstruction

As replacements for large-caliber, high-flow arteries such as the aorta, iliac, and femoral vessels, prosthetic grafts have excellent long-term patency and durability. Adjunctive antithrombotic therapy (above or beyond that recommended for PAD patients in general), is generally not necessary for the long term. In comparison, smaller caliber bypasses (femoral-popliteal/tibial) have a diminished long-term patency. Autogenous venous conduits are preferable over prosthetic grafts for these infrainguinal bypasses.

There are similarities and differences in the pathophysiology of thrombotic occlusion of vein grafts and arterial prostheses.¹²² The principal difference between thrombotic occlusion of vein bypasses and that of prosthetic bypasses has to do with surface thrombogenicity. Because they are lined with endothelium, vein grafts are inherently less thrombogenic than vascular prostheses, which almost never develop a complete endothelial lining. Vein grafts may lose variable amounts of their endothelial lining during harvesting and implantation, contributing to early thrombogenicity. This suggests the rationale for early antithrombotic therapy that could be discontinued after healing at anastomotic sites and repavement of the graft with endothelium. Prosthetic grafts, however, are highly thrombogenic at the time of implantation and remain so. Studies with ¹¹¹In-labeled platelets in humans demonstrate marked uptake on femoropopliteal bypass prostheses of Dacron or polytetrafluoroethylene (PTFE) but little or no uptake on vein bypasses in the same position.^{123,124}

Both vein and prosthetic grafts are subject to early occlusion from technical problems that reduce or disturb blood flow. Antithrombotic therapy might prevent or delay some of these occlusions. Both are also vulnerable to intermediate and late occlusions from neointimal hyperplasia and progression of atherosclerosis in the native vascular beds. However, the sites of neointimal hyperplasia differ for vein grafts and for vascular prostheses. In vein grafts, the process can be either diffuse, leading to progressive luminal reduction of the entire graft, or focal, causing isolated stenoses at anastomoses or valve sites.^{122,125} Prosthetic grafts, in contrast, are subject to the development of neointimal hyperplasia mainly at anastomoses, where the process arises from the adjacent artery. Patency of vein and prosthetic grafts is also adversely affected by progressive inflow and outflow atherosclerosis that reduces flow through the conduit. In the next section, we present a general review of the roles of postoperative heparin, and antiplatelet therapy, followed by individual analyses of the benefits of antithrombotic therapy for specific types of grafts.

3.2.1 Postoperative Heparin, Dextran, All Types of Lower-Extremity Reconstructions

Limiting adjunctive antithrombotic therapy to the early postoperative period might seem logical to counteract the early thrombogenicity of the graft, but this has not been borne out by clinical trials. Graft patencies (primarily venous grafts) at 1 month were unchanged by perioperative infusion of dextran 40 (vs no therapy), in two different trials totaling > 400 patients.^{126,127} A randomized trial of 314 patients undergoing femorodistal bypass showed no difference in 90-day patency with dextran 70 infusion compared to 7 days of postoperative LMWH.¹²⁸ Heart failure occurred in 12.8% of those receiving dextran 70.

Only three other major randomized trials have studied extended postoperative treatment with heparin to improve graft patency. Edmondson randomized 200 patients to LMWH (2,500 IU daily) or aspirin plus dipyridamole (325 and 300 mg/d) for 3 months.¹²⁹ Randomization was stratified according to indication for surgery. Kaplan-Meier estimate of graft patency showed 87% graft survival on LMWH and 72% on aspirin and dipyridamole at 6 months, and 78% vs 64% at 12 months. These overall differences did not achieve significance, except the subgroup operated for limb salvage in which LMWH was superior. This group accounted for most of the benefit of LMWH seen in the larger cohort. Unfortunately, the proportion of patients in this subgroup with prosthetic or vein grafts was not reported.

Another trial randomized 284 patients with critical limb ischemia to 5,000 IU LMWH or placebo daily for 3 months.¹³⁰ All patients also received aspirin (75 mg/d). Three-month patency rates were 83% and 80% for LMWH vs control, and 59% for both treatments at 1 year. Using higher doses of heparin, a third trial compared 10 days of postoperative treatment with LMWH (75 IU/kg q12h) vs. UFH (150 IU/kg q12h). Patency rates at 10 days were higher with the LMWH treatment, but patency data beyond 10 days were not collected, and 12% of patients in each group suffered major hemorrhage.

In summary, perioperative dextran does not appear to improve the long-term patency of bypass grafts and is associated with a significant risk of congestive heart failure. Because of wide variations in heparin dosage, associated antiplatelet therapy, and limited follow-up, the few studies of extended postoperative treatment with heparins are inconclusive.

3.2.2 VKAs, All Types of Lower-Extremity Reconstructions

A Cochrane systemic review of the use of anticoagulants to prolong the patency infrainguinal bypass grafts concluded that VKA may improve patency, but the evidence is not conclusive.¹³¹ Trials have not demonstrated a benefit in patient-important outcomes such as limb salvage, major thrombotic events, or QOL, and VKA is associated with increased bleeding risk.

Two randomized trials have compared the efficacy of VKA to no antithrombotic therapy in patients after infrainguinal bypass surgery.^{132,133} Kretschmer et al¹³² studied the effect of long-term treatment with VKA (target international normalized ratio [INR] 2.4–4.8), on vein graft patency, limb salvage, and survival in patients operated on for claudication or critical ischemia. Patency was determined by Doppler ultrasonography, and angiography when indicated. In 66 treated patients, 13 grafts were occluded (19.7%), compared with 23 grafts in 64 controls (35.9%), a relative risk of 0.55 (95% CI 0.30–0.99), with a proportional risk reduction of 45%. The corresponding absolute risk reduction by VKA was 16.2%. Limb loss was also significantly less common in the anticoagulated group (6.1% vs 20.3% in the control group). Among the anticoagulated patients, 27 (40.9%) died during 10 years of follow-up, compared with 37 patients (57.8%) in the control group (relative risk 0.71; 95% CI 0.49–1.01), with an absolute risk reduction of 16.9%. The study reported one fatal GI hemorrhage in the treated group.

A second trial included a more heterogeneous group of 116 patients undergoing various vascular

reconstructions (*ie*, vein or prosthetic bypass and endarterectomy).¹³³ Intention-to-treat analysis showed no difference in patency rate, limb salvage, and survival at the first, second, and third years of follow-up between the anticoagulated group and the controls. These conflicting results with the trial by Kretschmer may have been due to the lower level of anticoagulation (target INR 1.8–2.8) in the latter trial, or the differences in graft materials: vein in the first trial, and prosthetic grafts or endarterectomy in more than half of the patients in the second trial.

Two trials compared VKA with aspirin in patients undergoing a heterogeneous mix of vascular reconstructions. In 1979 Schneider et al¹³⁴ reported a trial of 91 patients with a vein femoropopliteal bypass and 122 patients after thromboendarterectomy. They were randomized to treatment with either aspirin (1,000 mg/d) or aspirin plus dipyridamole (225 mg/d) or VKA (target range not reported). The overall 2-year patency rate did not differ significantly in the groups, nor did rates of patient-important outcomes.

The Dutch BOA Study (Bypass, Oral Anticoagulants or Aspirin) randomized a total of 2,690 patients from 80 centers to VKA therapy (target INR 3–4.5) or 80 mg of aspirin daily.¹³⁵ All patients who required an infrainguinal bypass graft for obstructive arterial disease were eligible for inclusion, and the mean follow-up was 21 months. The VKA group had 308 graft occlusions, compared to 322 in the aspirin group (hazard ratio 0.95; 95% CI 0.82–1.11), suggesting no overall benefit of one treatment over the other. The hazard ratios of VKA vs aspirin were essentially the same in patients with femoropopliteal (hazard ratio 0.97; 95% CI 0.81–1.16) and femorocrural bypass grafts (hazard ratio 0.95; 95% CI 0.70–1.30). The composite outcome event of vascular death, MI, stroke, or amputation occurred 248 times in the VKA group and 275 times in the aspirin group (hazard ratio 0.89; 95% CI 0.75–1.06). Patients treated with VKA suffered significantly more major bleeding episodes than patients treated with aspirin: 108 vs 56 (hazard ratio 1.96; 95% CI 1.42–2.71). The optimal intensity of VKA therapy, *ie*, that intensity with the lowest incidence of both ischemic and hemorrhagic events, appeared to be an INR of 3–4.¹³⁶

Finally, Johnson et al¹³⁷ published the results of a multicenter Veterans Affairs Cooperative Trial in which 831 patients were stratified according to the type of bypass (vein or prosthetic graft) and randomized to treatment with low-intensity VKA (INR 1.4–2.8) plus aspirin 325 mg/d, or aspirin alone. Patency outcomes differed according to the graft type, so those results are presented below under the sections devoted to the specific graft type. Total mortality was higher in the VKA plus aspirin group (31.8%) than in the aspirin group (23%), risk ratio

1.41 (95% CI 1.09–1.84), which was surprisingly caused by an excess of malignancies in the group treated with combination therapy. There were no clear differences in vascular mortality and nonfatal ischemic events between the treatment groups. There were significantly more bleeding complications in the group with combination therapy than in the aspirin-alone group.

3.2.3 Antiplatelet Therapy, All Grafts

Overall, there is moderately strong evidence that antiplatelet therapy can extend the patency of peripheral bypass grafts. This issue is partly moot, however, because the general recommendation for antiplatelet therapy for all patients with PAD supersedes or overlaps with this recommendation for graft patency. In 1975, the first RCT showed the protective action of aspirin on thromboembolic events in patients after peripheral bypass surgery.¹³⁸ Six trials of antiplatelet therapy in patients with peripheral bypass grafts were described in the Sixth ACCP Consensus Conference on Antithrombotic Therapy.¹³⁹ These trials and others were pooled in the second part of the metaanalysis by the 1994 Antiplatelet Trialists' Collaboration.¹⁴⁰ All unconfounded randomized trials of antiplatelet therapy available before March 1990, in which vascular graft or native arterial patency was studied systematically, were included. In a metaanalysis of those 11, they demonstrated a significant risk reduction of graft occlusion of 32% in patients who were given platelet inhibitors.¹⁴⁰ A metaanalysis performed in 1999 of trials in infrainguinal bypass surgery¹⁴¹ found five trials comparing aspirin (alone or combined with other antiplatelet therapy) against placebo.^{142–146} In 423 patients treated with antiplatelet drugs, 120 bypasses occluded (28.4%), compared with 144 occlusions in 393 randomized controls (36.6%).¹⁴¹ The relative risk was 0.78 (95% CI 0.64–0.95), with a proportional risk reduction of 22%. This corresponds with an absolute risk reduction of 8.2%.

Recommendation

3.2. For all patients undergoing infrainguinal arterial reconstruction, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We recommend against the routine use of perioperative dextran, heparin, or long-term anticoagulation with VKA for all extremity reconstructions (Grade 1B).

3.3 Infrainguinal Autogenous Vein Bypasses

For femoral to popliteal or tibial artery bypasses, autogenous venous grafts have a superior longevity over prosthetic conduits. The superior patency of

vein grafts is supported primarily by a single, multicenter, randomized trial published in 1986, which compared saphenous vein grafts with expanded PTFE prostheses for lower-extremity arterial reconstructions.¹⁴⁷ The primary patency rate at 4 years for infrapopliteal bypasses with saphenous vein was 49%, significantly better than the 12% patency rate with PTFE bypasses ($p < 0.001$). Advances in surgical techniques have improved patency rates for both vein and prosthetic grafts, with vein grafts continuing to show superior patency. There are no major differences in outcomes between reversed and nonreversed *in situ* vein grafts, in which the valves are rendered incompetent.^{148,149}

3.3.1 Antiplatelet Therapy

A Cochrane systematic review of antiplatelet therapy to prolong the patency of peripheral grafts concluded that aspirin had a slight beneficial effect overall, with a weaker benefit for vein grafts.¹⁵⁰ Only three RCTs have directly compared aspirin (with dipyridamole) against no antiplatelet therapy for vein grafts. In 1984, Kohler et al¹⁴⁶ studied 71 patients with vein grafts and found no improvement in patency with long-term aspirin plus dipyridamole. Another single-center trial of 140 patients found that 6 weeks of postoperative aspirin plus dipyridamole conferred no benefit in 1-year patency for vein grafts.¹⁵¹ A larger, multicenter placebo-controlled trial of 559 patients found a cumulative 1-year and 2-year patency rates of 72% and 62% for placebo, and 78% and 70% for aspirin plus dipyridamole.¹⁴² The odds ratio favoring antiplatelet therapy at 1 year was 0.72 (95% CI 0.49–1.06) and at 2 years was 0.62 (95% CI 0.44–89). Overall, these differences in graft patency were not statistically significant, but subsequent MIs or strokes were significantly reduced by antiplatelet therapy in this population.

Ticlopidine has been shown to be effective in improving the patency of femoropopliteal and femorotibial bypasses. In a randomized, multicenter, placebo-controlled trial of 243 patients, primary patency at 24 months was 82% in the ticlopidine group and 63% in the placebo group ($p = 0.002$).¹⁵² In clinical use, ticlopidine has now been superseded by the chemically related drug clopidogrel, for which new trials are underway. At present, there are no definitive data to recommend clopidogrel to improve patency, and clopidogrel has not been directly compared to aspirin.

Controversy still remains as to whether antiplatelet therapy is best started pre- or postoperatively, although the weight of evidence suggests inhibition of platelet function is best established prior to the vascular injury. Two of three trials of aspirin showed

a benefit in graft patency when the drug was started preoperatively,^{144,145} and the third showed no benefit when antiplatelet therapy was begun postoperatively.¹⁴⁶ This third trial had the largest percentage of vein grafts, which are thought to be less thrombogenic. Data from the literature on the patency of aortocoronary saphenous vein grafts supports the concept of beginning antiplatelet therapy prior to surgery.^{153–156}

3.3.2 VKAs

In the mixed group of vascular reconstructions studied by Schneider et al,¹³⁴ a subgroup analysis of vein bypass patients demonstrated a better patency rate in the group treated with VKA compared with both antiplatelet groups: 87% vs 65%, $p < 0.005$. In the subgroup of patients undergoing thromboendarterectomy, antiplatelet therapy proved to be favorable compared to VKA; patency rates were 80% and 51%, respectively, $p < 0.002$.

The Dutch BOA trial performed a *post hoc* subgroup analysis of outcomes according to graft material. This showed a lower risk of vein graft occlusion in patients receiving VKA than in those receiving aspirin (hazard ratio 0.69; 95% CI 0.54–0.88). Seventeen patients would require treatment to prevent one occlusion. Patients treated with VKA suffered significantly more major bleeding episodes than patients treated with aspirin: 108 vs 56 episodes (hazard ratio 1.96; 95% CI 1.42–2.71).

Johnson's Veterans Affairs Cooperative Trial (see previously) stratified patients according to the proposed type of bypass (vein or prosthetic graft) before randomization, and assigned treatment with low-intensity VKA (INR 1.4–2.8) plus aspirin 325 mg/d, or aspirin alone.¹³⁷ The average follow-up was 39.3 months in the vein bypass group. VKA plus aspirin conferred no benefit in patency over aspirin alone. Fifty-seven of 231 venous grafts (24.7%) occluded in the group with combination therapy, compared with 57 of 227 grafts (25.1%) in the aspirin group (risk ratio 1.04; 95% CI 0.72–1.51). Subgroup analysis according to length of bypass did not show any difference either, although there was a trend in favor of VKA plus aspirin in patients who received a pedal bypass.

Sarac et al¹⁵⁷ tested a more complex antithrombotic management strategy for a selected group of 56 patients with vein bypasses considered to be at high risk for thrombosis. Patients with a suboptimal venous conduit, poor arterial run-off, or reoperative grafting were randomized to a comprehensive postoperative anticoagulation regimen, or aspirin. All patients received preoperative aspirin. One group was treated with IV UFH immediately postopera-

tively (target activated partial thromboplastin time 1.5 times control), until long-term treatment with VKA (target INR 2–3) and aspirin were instituted. The other group received postoperative aspirin (325 mg/d). The cumulative 3-year primary rates were significantly greater in the comprehensive anticoagulation regimen (UFH/VKA/aspirin) vs the aspirin group (74% vs 51%). The primary-assisted and secondary patency rates were similarly favorable for the VKA group. However, these benefits came at the expense of a significantly higher rate of wound hematomas and reoperations for bleeding (32% vs 3.7%).

3.3.3 Summary

It is difficult to extract a clear message from the data of the few randomized studies of vein bypasses because no two trials have compared the same antithrombotic strategies, and several trials suffer from the liabilities of *post hoc* subgroup analysis. As mentioned above, the routine use of perioperative aspirin is not controversial because it is highly recommended to prevent general cardiovascular morbidity and mortality in the PAD patient population. Long-term aspirin therapy may offer a weak benefit in prolonging the patency of routine vein grafts, but again the issue is moot because aspirin is already recommended for all PAD patients. For routine vein grafts, the value of VKA to prolong patency appears to be weak. The VA Cooperative Trial, which preoperatively stratified patients according to graft type, found no benefit in the addition of warfarin to aspirin for vein grafts. Subgroup analysis of the Dutch BOA trial found that VKA alone prolonged vein graft patency better than aspirin alone, but at the expense of more hemorrhagic complications. The conclusions of the Sarac et al trial¹⁵⁷ (and trends from the VA trial) may point the way to a future, preferred strategy for vein grafts: development of individualized antithrombotic regimens, based on a clinical stratification of the risk of bypass occlusion.

Recommendation

3.3. For patients receiving routine autogenous vein infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) (Grade 1A). We suggest that VKA not be used routinely in patients undergoing infrainguinal vein bypass (Grade 2B). For those at high risk of bypass occlusion and limb loss, we suggest VKA plus aspirin (Grade 2B).

Values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

3.4 Infrainguinal Prosthetic Grafts

In the absence of suitable venous conduits, placement of arterial prostheses may be necessary. Most randomized trials evaluating available materials indicate that human umbilical vein grafts have a slightly better patency than PTFE prostheses, which in turn are comparable to dacron materials.^{158–162} However, many surgical and technical factors go into the choice of prosthetic conduit, and the vast majority of infrainguinal prosthetic grafts are currently dacron or PTFE. The diameter of the PTFE graft is known to be an independent risk factor for thrombosis, as grafts < 7 mm in diameter have lower patency rates.^{158,162}

3.4.1 Antiplatelet Agents

Antiplatelet therapy affects prosthetic and vein grafts differently. A favorable effect of antiplatelet therapy was demonstrated in the trials studying patients with prosthetic grafts,^{143–145} whereas trials in which at least 70% had venous grafts were inconclusive.^{142,146} This stronger beneficial effect of aspirin on prosthetic grafts was also supported in a trial by Clyne et al¹⁵¹ in which aspirin and dipyridamole were given for only 6 weeks postoperatively. They demonstrated a benefit of antiplatelet treatment in patients with prosthetic grafts, whereas no benefit was seen in the vein graft bypass group. The beneficial effect of antiplatelet therapy on prosthetic graft patency has been supported by a meta-analysis of all trials since 1999.¹⁶³ The Dutch BOA study (see previously) compared antiplatelet therapy with aspirin to VKA alone.¹³⁵ In the subgroup of 1,100 patients with prosthetic grafts, VKA was inferior to aspirin (hazard ratio 1.32, 95% CI 0.81–2.15). There are no data indicating which antiplatelet drug(s) might be most effective. In the Antiplatelet Trialists' Collaboration overview of all antiplatelet studies, neither direct nor indirect comparisons of the effects of different regimens (aspirin, dipyridamole, sulfipyrazone, ticlopidine and suloctidil) on vascular patency provided convincing evidence that one antiplatelet regimen was more effective than another.¹⁴⁰

3.4.2 VKAs

Only two major trials have examined the value of VKA in extending the patency of prosthetic bypasses. In the VA Cooperative trial, the average follow-up was 36.6 months in the group that received prosthetic grafts. All patients received aspirin preoperatively. In patients with prosthetic bypasses, 44 occlusions (23.5%) occurred in patients with VKA plus aspirin vs 64 occlusions (34.4%) in patients treated with aspirin (risk ratio 0.62; 95% CI 0.42–0.92).

Aspirin plus VKA resulted in a 38% proportional risk reduction for graft failure. This effect was due primarily to the difference found in the 212 patients with 6-mm bypasses (mostly femoropopliteal above knee), a graft diameter known to be more prone to early failure.

Total mortality in the VA Cooperative trial was higher in the VKA-plus-aspirin group (31.8%) than in the aspirin group (23%) [risk ratio 1.41; 95% CI 1.09–1.84], which was inexplicably caused by an excess of malignancies in the group treated with combination therapy. There were no clear differences in vascular mortality and nonfatal ischemic events between the treatment groups. There were significantly more bleeding complications in the group with combination therapy than in the aspirin alone group.

The Dutch BOA Study randomized ~ 1,100 patients with nonvenous grafts to VKA therapy (target INR 3–4.5) or 80 mg/d of aspirin.¹³⁵ Treatment was started within 5 days after surgery, and approximately one third of patients were receiving aspirin preoperatively. The mean follow-up was 21 months. The risk of prosthetic graft occlusion was lower in patients treated with aspirin (hazard ratio 1.26; 95% CI 1.03–1.55). Fifteen patients would require treatment to prevent one occlusion. Patients treated with VKA suffered significantly more major bleeding episodes than patients treated with aspirin: 108 vs 56 (hazard ratio 1.96; 95% CI 1.42–2.71). The optimal intensity of VKA therapy, *ie*, that intensity with the lowest incidence of both ischemic and hemorrhagic events, appeared to be an INR of 3–4.¹³⁶

Recommendation

3.4. For patients receiving routine prosthetic infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We suggest that VKA not be used routinely in patients undergoing prosthetic infrainguinal bypass (Grade 2A).

Values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

4.0 CAROTID ENDARTERECTOMY

4.1 Antiplatelet Therapy

Aspirin therapy is an important adjunct to carotid endarterectomy. The goal of antithrombotic therapy in this setting is to prevent immediate, perioperative, and long-term neurologic complications stemming from thrombus formation at the endarterectomy site.

Scintigraphic studies with indium-111 labeled platelets document marked deposition of platelets at the endarterectomy site immediately after operation.^{164,165} The intensity of platelet accumulation decreases over time, possibly because of reendothelialization of the endarterectomy site. In one study of 22 patients, treatment of patients undergoing carotid endarterectomy with aspirin plus dipyridamole significantly decreased indium-111 platelet deposition and appeared to decrease the incidence of perioperative stroke.¹⁶⁵ In a study of 125 patients assessing the benefit of aspirin therapy for longer periods after carotid endarterectomy¹⁶⁶ patients receiving aspirin, 650 mg bid started on the fifth postoperative day had a slight but significant reduction in unfavorable endpoints when considered together (continuing TIAs, stroke, retinal infarction, and death from stroke) during a 2-year follow-up period in comparison with control subjects receiving placebo. This experience contrasts with that of a randomized trial of 301 patients comparing low-dose aspirin therapy, 50–100 mg/d, with placebo after carotid endarterectomy.¹⁶⁷ Therapy was started 1 week to 3 months after operation and no significant benefit of low-dose aspirin therapy was detectable. However, the timing of perioperative aspirin therapy may be critical, with late postoperative initiation of therapy being too late to be beneficial. This is suggested by a randomized, double-blind trial of aspirin vs placebo in 232 patients; where therapy was started preoperatively and was associated with a marked reduction in intra- and postoperative stroke.¹⁶⁸

The Aspirin and Carotid Endarterectomy (ACE) Trial was a multicenter, randomized, blinded clinical trial in which 2849 patients scheduled for carotid endarterectomy were randomly assigned to one of four aspirin doses (81 mg, 325 mg, 650 mg, and 1,300 mg).¹⁶⁹ 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 mg and 325 mg) than in the high-dose groups at 30 days (5.4% vs 7.0%, $p = 0.07$) and at 3 months (6.2% vs 8.4%, $p = 0.03$). Since many patients would be taking higher doses of aspirin prior to randomization into the study, and surgery would be performed prior to washout of the previous dose platelet effect, a separate efficacy analysis was performed of patients previously taking < 650 mg aspirin and who were randomized ≥ 2 days before surgery. In the efficacy analysis, there were 566 patients in the low-dose group, and 550 in the high-dose group. The combined rate of stroke, MI, and death occurred less frequently in the low-dose group than in the high-dose group at both 30 days and 3 months (3.7% vs 8.2%, $p = 0.002$; and 4.2% vs 10.0%, $p = 0.0002$).¹⁶⁹

No RCTs have evaluated the value of clopidogrel

in preventing perioperative stroke during carotid endarterectomy. The randomized trial by Payne et al¹⁷⁰ compared dual antiplatelet therapy with clopidogrel (75 mg preoperatively) and aspirin (150 mg) vs aspirin alone prior to endarterectomy, but they did not record any neurologic end points. The addition of clopidogrel did, however, significantly impair surgical hemostasis as judged by the time required for surgical closure.

Based on these considerations, perioperative aspirin therapy, 75–100 mg/d, can be recommended in patients undergoing carotid endarterectomy. Therapy should be started at the time of clinical presentation and continued through the perioperative period. Bleeding complications, particularly wound hematomas, occur in 1.4 to 3.0% of patients undergoing carotid endarterectomy and are associated with nonreversal of intraoperative UFH, hypertension, and perioperative antiplatelet therapy.^{171,172} If intraoperative UFH is not fully reversed or continuous UFH anticoagulation is administered postoperatively, perioperative aspirin therapy would potentially increase the incidence of hematomas and other bleeding complications.

Recommendation

4.0. In patients undergoing carotid endarterectomy, we recommend that aspirin, 75–100 mg, be given preoperatively to prevent perioperative ischemic neurologic events. We recommend lifelong postoperative aspirin (75–100 mg/d) [Grade 1A].

5.0 ASYMPTOMATIC CAROTID STENOSIS

It is unknown whether aspirin therapy will prevent or delay the onset of TIAs and strokes in patients with asymptomatic cerebrovascular disease. Indirect evidence from the Veterans Administration Asymptomatic Carotid Stenosis study (ACAS) suggests that aspirin may be beneficial in patients with advanced stenosis who do not undergo carotid endarterectomy.^{173,174} A surprising 16% of patients randomized to medical therapy were intolerant and had to discontinue aspirin. The incidence of neurologic events was significantly higher among patients who stopped taking aspirin.

The long-term protective effects of aspirin on stroke rate for asymptomatic patients with $\geq 50\%$ carotid stenosis is unclear. In a blinded, placebo-controlled trial in which 372 asymptomatic patients with $\geq 50\%$ carotid stenosis were randomized to either aspirin (325 mg/d) or placebo, no difference in stroke rate or incidence of a composite end point of ischemic events was observed at a mean follow-up of

2.3 years.¹⁷⁵ The clinical application of these findings, particularly concerning the use of aspirin in these patients as a means of preventing cardiac events, is tempered by the relatively short follow-up period and by the exclusion of patients with symptomatic cerebrovascular disease, recent MI, and unstable angina.

The value of dual antiplatelet therapy to prevent cerebro- or cardiovascular morbidity and mortality has been called into question by the MATCH and CHARISMA trials.^{24,25} MATCH studied patients with recent cerebrovascular events and extra vascular risk factors for a broad composite end point of cardiovascular morbidity and mortality. Aspirin plus clopidogrel marginally reduced this end point (15.7%) compared to clopidogrel alone (16.7%; absolute risk reduction 1% [95% CI 0.6 to 2.7]). However, both life-threatening and major bleeding complications were higher with dual therapy. CHARISMA compared the same dual antiplatelet therapy to aspirin alone and found no significant difference in a similar composite end point.

A significant stenosis may recur at the site of carotid endarterectomy in as many as 10 to 19% of patients after surgery.¹⁷⁶ Because the risk of progression to stroke or occlusion is considered low, intervention is generally recommended only for the small subset of patients who develop cerebrovascular symptoms.¹⁷⁷ Data from retrospective studies suggest that antiplatelet therapy does not reduce the incidence of recurrent carotid artery stenosis.^{178,179} A randomized trial confirmed that treatment with aspirin and dipyridamole does not prevent recurrent stenosis after carotid endarterectomy.¹⁸⁰ Although there are no data to recommend aspirin treatment to prevent disease progression or symptom development in patients with asymptomatic carotid stenosis (primary or recurrent), these patients do have a high prevalence of associated coronary and PAD. Therefore, antiplatelet therapy may improve their overall long-term cardiovascular outcomes.

Recommendation

5.0. In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), we recommend lifelong aspirin, 75–100 mg/d (Grade 1C). In this patient group, we recommend against dual antiplatelet therapy with aspirin and clopidogrel (Grade 1B).

6.0 LOWER-EXTREMITY ENDOVASCULAR PROCEDURES

Recommendations for optimal antithrombotic therapy for lower extremity arterial endovascular

interventions are hampered by the lack of agreement over the proper role of these procedures, and a lack of data from randomized clinical trials. There is general consensus that transluminal angioplasty is appropriate for focal stenotic lesions of the iliac and femoropopliteal arteries, particularly when the indication for limb revascularization is intermittent claudication rather than critical ischemia, and in nondiabetic patients with relatively preserved tibial artery runoff.^{181,182} There is less agreement regarding the suitability of transluminal angioplasty for more diffuse and extensive patterns of occlusive disease.

Complicating the matter further is the “moving target” of evolving catheter-based technologies. The use of self-expanding metallic stents can salvage what otherwise might be an unacceptable technical outcome from balloon angioplasty alone. Testing of newer devices such as medication-coated stents and atherectomy devices in the lower extremity arterial circulation is under way.^{183,184} Based on the promising early results seen with coronary stenting,¹⁸⁵ such devices might find a role in the peripheral arterial vascular bed, although the causes of stenosis and occlusion of stents placed in the lower limb arteries may not be the same as the causes for failure of coronary stents. Nor can the results from clinical trials evaluating antithrombotic therapy for balloon angioplasty alone necessarily be extrapolated to newer stent devices or disobliterative procedures.

Life-long antiplatelet therapy is already recommended for all patients with PAD on the basis of their increased risk of coronary and cerebrovascular events. Given this, the primary issue governing lower-extremity balloon angioplasty is whether any agent improves the patency of the treated arteries. This has been addressed in two metaanalyses that found the data to be equivocal.^{186,187} Of the studies reviewed, two RCTs compared combinations of aspirin and dipyridamole with placebo.^{188,189} In a single-center trial of 199 patients undergoing lower-extremity angioplasty, patients were randomized to a combination of dipyridamole (225 mg) plus high-dose aspirin (990 mg), dipyridamole with low-dose aspirin (300 mg), or placebo.¹⁸⁸ Only patients undergoing successful balloon angioplasty of femoropopliteal arterial segment atherosclerotic obstructive lesions were randomized. Clinical and angiographic follow-up showed an improvement in both treatment groups in comparison with placebo; however, only the high-dose aspirin group achieved a statistically significant improvement.

In another RCT from 12 centers, 223 patients undergoing balloon angioplasty of iliac and femoropopliteal segments were randomized to either placebo or a combination of aspirin (50 mg) and dipyridamole (400 mg).¹⁸⁹ Primary patency and over-

all results were the same in both groups, thus showing no benefit with antiplatelet therapy. Limitations of this study include a higher percentage of patients undergoing treatment of more favorable iliac lesions in the placebo group (65% vs 51%); adjunctive use of metallic stents was not performed, as is now commonly done in clinical practice.

After femoropopliteal or tibial artery balloon angioplasty, anticoagulation is frequently combined with antiplatelet therapy, although the results of the three RCTs do not support this practice.^{190–192} A total of 438 patients were randomized in the three studies. In all three studies the arterial patency rates were slightly lower in the anticoagulation groups, but this was not statistically significant. Also, there tended to be more bleeding complications in the anticoagulation groups, including one fatal intracerebral hemorrhage. A recent trial of 275 patients undergoing femoropopliteal angioplasty compared three months of adjunctive LMWH plus long-term aspirin, vs long-term aspirin.¹⁹³ The addition of LMWH did not reduce the overall incidence of occlusion or restenosis, although the subgroup with more severe occlusive disease may have benefited.

For coronary stenting, the value of dual antiplatelet therapy (clopidogrel plus aspirin) to prevent occlusion and early restenosis is well established (see the “Primary and Secondary Prevention of Chronic CAD” chapter in this supplement). However, such combinations have not been studied in RCTs of interventions in the peripheral circulation. There are important enough differences between peripheral arterial interventions and those in the coronary circulation to be skeptical when extrapolating experience from one anatomic region to another. Still, in the absence of site-specific data, dual antiplatelet therapy is common clinical practice for lower extremity balloon angioplasty and stenting, especially the femoropopliteal and tibial segments. Likewise, in carotid artery stenting, aspirin plus clopidogrel was standard therapy (preprocedure and at least 30 days after) for two major RCTs of carotid stenting.^{194,195}

In summary, the evidence supporting antiplatelet therapy to specifically prolong the patency of peripheral arterial endovascular procedures is weak, but aspirin is still indicated for all patients with PAD, including those undergoing lower-extremity balloon angioplasty (with or without stenting). Beyond aspirin, there are insufficient data to recommend any additional antiplatelet or antithrombotic agents for iliac artery angioplasty and stenting. Similarly, insufficient data exist to recommend additional antithrombotic agents in the setting of femoropopliteal, tibial (or carotid) angioplasty and stenting. Specifically, the addition of anticoagulation to antiplatelet therapy does not appear to convey any advantage and

increases the risk of bleeding complications. However, it is reasonable to consider short- or intermediate-term dual antiplatelet therapy with aspirin and thienopyridines for higher-risk infrainguinal or carotid stenting, given the relatively high rate of failure of lower-extremity interventions, and the clinical consequences of stroke after carotid stenting.

Recommendation

6.0. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin (75–100 mg/d) [Grade 1C]. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend against anticoagulation with heparin or VKA (Grade 1A).

ACKNOWLEDGMENT: The authors thank Daniel B. Mark, MD, for his contributions to the analysis of resource allocations in antiplatelet therapy for PAD.

CONFLICT OF INTEREST DISCLOSURES

Dr. Sobel discloses that he has received grant monies from the National Institutes of Health and the Department of Veterans Affairs.

Professor Verhaeghe discloses that he has received grant monies from Bayer, LEO Pharma, and Sanofi-Aventis.

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Chest 2008;133; 815S-843S

DOI 10.1378/chest.08-0686

This information is current as of July 17, 2009

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