Antithrombotic Therapy in Peripheral Arterial Occlusive Disease

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about antithrombotic therapy for peripheral arterial occlusive disease is part of the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs, and Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004;126:179S–187S*). Among the key recommendations in this chapter are the following: For patients with chronic limb ischemia, we recommend lifelong aspirin therapy in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease (Grade 1A) and in those without clinically manifest coronary or cerebrovascular disease (Grade 1C+). We recommend clopidogrel over no antiplatelet therapy (Grade 1C+) but suggest that aspirin be used instead of clopidogrel (Grade 2A). For patients with disabling intermittent claudication who do not respond to conservative measures and who are not candidates for surgical or catheter-based intervention, we suggest cilostazol (Grade 2A). We suggest that clinicians not use cilostazol in patients with less-disabling claudication (Grade 2A). In these patients, we recommend against the use of pentoxifylline (Grade 1B). We suggest clinicians not use prostaglandins (Grade 2B). In patients with intermittent claudication, we recommend against the use of anticoagulants (Grade 1A). In patients with acute arterial emboli or thrombosis, we recommend treatment with immediate systemic anticoagulation with unfractionated heparin (UFH) [Grade 1C]. We also recommend systemic anticoagulation with UFH followed by long-term vitamin K antagonist (VKA) in patients with embolsim [Grade 1C]). For patients undergoing major vascular reconstructive procedures, we recommend UFH at the time of application of vascular cross-clamps (Grade 1A). In patients undergoing prosthetic infrainguinal bypass, we recommend aspirin (Grade 1A). In patients undergoing infrainguinal femoropopliteal or distal vein bypass, we suggest that clinicians do not routinely use a VKA (Grade 2A). For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, we recommend against VKA plus aspirin (Grade 1A). For those at high risk of bypass occlusion and limb loss, we suggest VKA plus aspirin (Grade 2B). In patients undergoing carotid endarterectomy, we recommend aspirin preoperatively and continued indefinitely (Grade 1A). In nonoperative patients with asymptomatic or recurrent carotid stenosis, we recommend lifelong aspirin (Grade 1C+). For all patients undergoing extremity balloon angioplasty, we recommend long-term aspirin (Grade 1C+).

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Abbreviations: ACD = absolute claudication distance; BOA = Bypass, Oral Anticoagulants or Aspirin; CI = confidence interval; INR = international normalized ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; PAOD = peripheral arterial occlusive disease; PGE_1 = prostaglandin E_1; PGI_2 = prostaglandin I_2; RCT = randomized controlled trial; rt-PA = recombinant tissue-type plasminogen activator; STILE = Surgery vs Thrombolysis for Ischemia of the Lower Extremity; TIA = transient ischemic attack; UFH = unfractionated heparin; TOPAS = Thrombolysis or Peripheral Arterial Surgery; VKA = vitamin K antagonist

Patient populations with peripheral arterial occlusive disease (PAOD) are summarized in Table 1.

1.0 Chronic Limb Ischemia

Atherosclerotic PAOD is symptomatic with intermittent claudication in 2 to 3% of men and 1 to 2% of women > 60 years old.[1–3] However, the prevalence of asymptomatic PAOD, 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 remain unchanged or improved, 20 to 30% have progression of symptoms and require intervention, and 10% require amputation.[6,7] Progression of disease is greatest in patients with multilevel arterial involvement, low ankle-to-brachial pressure indices, chronic renal insufficiency, diabetes mellitus and, possibly, heavy smoking.[6]

The prevalence of PAOD increases with age and is a significant cause of hospital admission and an important predicator of cardiovascular and stroke mortality, which is increased twofold to threefold.[1,2,8,9] 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.

This chapter addresses antithrombotic therapy for patients with PAOD. We note, however, that a systematic

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review and metaanalysis[10] of randomized trials of exercise therapy in patients with claudication suggests that exercise improves maximal walking time by 150%. One must judge symptomatic antithrombotic therapy in this context. Furthermore, while risk factor modification is not well studied in patients with PAOD, observational data and generalization from trials[11,12] in persons with other manifestations of cardiovascular disease support the importance of treating key risk factors such as smoking, diabetes, dyslipidemia, and hypertension.[1]

1.1 Antiplatelet therapy

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

A compelling reason to administer antiplatelet therapy to patients with PAOD is to prevent death and disability from stroke and myocardial infarction (MI). The Antithrombotic Trialists' Collaboration metaanalysis[13] found that among 9,214 patients with PAOD 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. 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.

1.1.1 Aspirin

The antiplatelet trialists analysis[13] 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. Data from a single randomized controlled trial (RCT)[14] suggest that aspirin, alone or combined with dipyridamole, will delay the progression of established arterial occlusive disease as assessed by serial angiography. This may have been an effect on inhibiting thrombotic occlusion of stenotic vessels rather than retarding stenosis progression.

In another study of 54 patients with intermittent claudication, the combination of aspirin and dipyridamole was found to increase the pain-free walking distance and resting limb blood flow.[15] An RCT[16] 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. The Physicians Health Study,[17] a primary prevention study, found that aspirin, 325 mg every other day, decreased the need for peripheral arterial reconstructive surgery; however, no difference was noted between the aspirin and placebo groups in the development of intermittent claudication.

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. Almost all patients with PAOD who do not have clinically manifest disease have occult coronary or cerebrovascular disease. Aspirin is less effective than ticlopidine and clopidogrel (see below). However, the marginal benefit of these other drugs is small, and aspirin is much less expensive. These are the rationales for our recommendation for aspirin over clopidogrel.

Recommendation

1.1.1. We recommend lifelong aspirin therapy (75 to 325 mg/d) in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease (**Grade 1A**) and in those without clinically manifest coronary or cerebrovascular disease (**Grade 1C+**).

1.1.2 Ticlopidine

One metaanalysis[18] 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. Ticlopidine has also shown a modest beneficial effect for relieving symptoms, increasing walking distance, and improving lower-extremity ankle pressure indices in patients with intermittent claudication (see chapter by Patrono et al in this Supplement).[19–20] In a multicenter, placebo-controlled RCT,[21] ticlopidine, 250 mg/d, resulted in fewer vascular surgery procedures (relative risk, 0.49; $p < 0.001$) among patients with intermittent claudication. However, ticlopidine is associated with a substantial risk of leukopenia and thrombocytopenia, requiring close hematologic monitoring. Because of these side effects, clopidogrel has replaced ticlopidine as the thienopyridine of choice.

Recommendation

1.1.2. We recommend clopidogrel over ticlopidine (**Grade 1C+**).

1.1.3 Clopidogrel

Clopidogrel is a thienopyridine, the chemical structure of which is similar to ticlopidine, that exerts an irreversible antiplatelet effect primarily directed against adenosine diphosphate-induced stimulation of platelet function (see chapter by Patrono et al in this Supplement). In a large, multicenter RCT[22] of 19,185 patients, investigators compared the relative efficacy of clopidogrel and aspirin in reducing the risk of a composite end point of ischemic stroke, MI, or vascular death. The study population comprised patients with recent ischemic stroke, recent MI, or PAOD. The overall incidence of composite end points was lower in the group treated with clopidogrel (5.32%/yr) than with aspirin (5.83%; $p = 0.043$). A subgroup analysis suggested that a larger benefit of clopidogrel over aspirin in patients with symptomatic PAOD than those with

Table 1—*PAOD Patients*

Section	Population	Interventions or Exposures	Outcome	Methodology
1.1.1–1.1.3	Chronic limb ischemia and claudication	Antiplatelet therapy (clopidogrel, ticlopidine, aspirin)	Survival; ischemic stroke, MI, vascular death, walking distance	RCTs
1.1.4–1.1.5	Chronic limb ischemia and claudication	Cilostazol, pentoxifylline	Improvement in maximum walking distance, absolute claudication distance, walking impairment questionnaire, health-related quality of life	RCTs
1.1.6	Chronic limb ischemia and claudication	Prostaglandins	Improvement in maximum walking distance, absolute claudication distance, walking impairment questionnaire, health-related quality of life	RCTs
1.1.7	Chronic limb ischemia	Ketanserin, suloctidil, fish oil supplementation, naftidrofuryl, picotamide, heparins, warfarin	Survival; composite end point of ischemic stroke, MI, vascular death, improvement in maximum walking distance, absolute claudication distance, walking impairment questionnaire, health-related quality of life	RCTs
2.1–2.2	Acute limb ischemia	Anticoagulation, intra-arterial thrombolytic therapy	Limb salvage, survival	RCTs; observational studies
3.1	Vascular surgery	Intraoperative heparin anticoagulation	Graft patency, fatal/nonfatal MI	RCTs
3.2.1	Infrainguinal prosthetic bypass	Aspirin, clopidogrel, ticlopidine, warfarin	Graft patency, limb salvage, survival	RCTs
3.2.2	Infrainguinal vein bypass	Aspirin, clopidogrel, ticlopidine, warfarin	Graft patency, limb salvage, survival	RCTs
3.2.3	Infrainguinal bypass at high thrombotic risk	Aspirin plus warfarin	Graft patency, limb salvage	RCTs
4.1.	Carotid endarterectomy	Aspirin	Stroke, MI, death	RCTs
5.0	Asymptomatic and recurrent carotid stenosis	Aspirin	Stroke, MI, death	RCTs
6.0	Lower-extremity endovascular procedures	Antiplatelet agents (all), anticoagulation	Limb salvage, arterial patency, stroke, MI, death	RCTs

cardiac or cerebrovascular disease. Subgroup analysis is often misleading, and we are inclined to trust the overall estimate of clopidogrel effectiveness in all patients with vascular disease.

Recommendation

1.1.3. We recommend clopidogrel in comparison to no antiplatelet therapy (**Grade 1C+**) but suggest that aspirin be used instead of clopidogrel (**Grade 2A**).

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

1.1.4 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. We found no systematic reviews on this drug for PAOD. Several published clinical trials that have evaluated the efficacy of cilostazol as a therapeutic agent for intermittent claudication.

In the first of these published trials,[23] 239 patients randomly assigned to receive a 16-week course of cilostazol or placebo, the cilostazol group showed an increase in absolute claudication distance (ACD) of 47%, while the control group improved by 13% ($p < 0.001$). Functional status assessment also showed improvement with cilostazol compared with control subjects, although there were significantly more side effects with cilostazol, most notably headache (30%) and diarrhea (12.6%).

In a smaller trial[24] of 12 weeks of cilostazol or placebo, the ACD increased 31% with cilostazol, vs a drop of 9% with placebo ($p < 0.01$). In another study,[25] 45 patients with claudication were randomly assigned to one of three groups, cilostazol, pentoxifylline, or placebo for 24 weeks; at 24 weeks, the treatment was changed to placebo for all groups, and follow-up was continued for 6 more weeks. There was a more significant decrease in ACD after cessation of cilostazol therapy than with either pentoxifylline or placebo. The increase in ACD from baseline was similar in both the cilostazol and pentoxifylline groups (109% and 94%, respectively).

In a trial[26] of 516 patients randomly assigned to cilostazol (100 mg bid or 50 mg bid) or placebo therapy for 24 weeks, those receiving 50 mg bid had a 38% and 48% mean improvement in maximal and pain-free walking distance, respectively, while with a dose of 100 mg bid showed a 51% and 59% improvement, respectively, compared to placebo. Benefit was noted as early as 4 weeks, with progressive improvement over the 24-week period of the trial. There was also a significant improvement in functional outcomes with cilostazol, and no difference in the incidence of adverse events in the three groups. Side effects noted in each of the studies included headache, loose and soft stools, diarrhea, dizziness, and palpitations.

Cilostazol is more effective than pentoxifylline, as illustrated in a study of 698 patients randomized to pentoxifylline (400 mg tid), cilostazol (100 mg bid), or placebo for 24 weeks.[27] In comparison to pentoxifylline, cilostazol produced a significant increase in walking distance for onset of claudication (218 m for cilostazol vs 202 m for pentoxifylline, $p = 0.0001$) and 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 thus appears to be an appropriate therapy for patients with disabling claudication who are not candidates for revascularization. However, its high cost, modest effect on walking distance, lack of demonstrated benefit in improving health-related quality of life, and the salutary effects of exercise therapy and risk factor modification argue against its routine use in patients with less-disabling intermittent claudication.

Cilostazol has weak platelet inhibitory effects, and there are no data to support its use as an antiplatelet agent. Antiplatelet therapy with aspirin or clopidogrel should be continued in patients receiving cilostazol.

Recommendation

1.1.4. For patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention, we suggest cilostazol (**Grade 2A**). We suggest that clinicians **not** use cilostazol in those with less-disabling claudication (**Grade 2A**).

Underlying values and preferences: The recommendation against cilostazol for those with less-disabling claudication places a relatively low value on small possible improvements in function in the absence of clear improvement in health-related quality of life.

1.1.5 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.[28–30] One metaanalysis[31] suggests that pentoxifylline improves walking distance by 29 m compared with placebo, although the improvement was approximately 50% in the placebo group, and use of pentoxifylline improved walking distance by an additional 30%. Moreover, clinical trials have shown conflicting results. Some[32–37] have concluded that pentoxifylline was significantly more effective than placebo in improving treadmill-walking distance, but others[38–43] could not demonstrate consistent benefit. 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.[44] 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 PAOD.[45,46]

Recommendation

1.1.5. We recommend **against** the use of pentoxifylline (**Grade 1B**).

1.1.6 Prostaglandins

Prostaglandins with antiplatelet and vasodilatory effects, such as prostaglandin E_1 (PGE_1) and prostaglandin I_2 (PGI_2), have been administered IV or intra-arterially to patients with advanced chronic arterial insufficiency in hopes of relieving rest pain and healing ischemic ulcers. In a study[47] of 80 patients with intermittent claudication, IV administration of a PGE_1 produced a dose-related improvement in walking distance and quality of life at 4 weeks and 8 weeks. In an older but larger randomized, blinded, multicenter trial[48] of patients with one to three ischemic ulcers not healing for 3 weeks with standard care who were randomized to receive either PGE_1 or a placebo for 72 h through a central venous catheter, PGE_1 was found to be ineffective. In a small, randomized open study,[49] PGE_1 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. The largest data set comes from a multicenter RCT[50] in which 1,560 patients with chronic critical ischemia of the leg were randomly assigned to receive either a daily IV infusion of PGE_1 or nothing (open-label study) during their hospital stay. At discharge, there was a greater reduction in composite outcome events in the PGE_1 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 PGE_1 prodrug, was evaluated in a small randomized trial[51] of 80 patients with claudication, and was associated with an increase of 35 m in maximal walking distance after 8 weeks of treatment, compared with a slight decrease in placebo-treated control subjects. This difference was statistically significant ($p < 0.01$), although the clinical significance of the increase was marginal.

A blinded trial that contained a high proportion of diabetics showed no beneficial effect of IV PGI_2 on ulcer healing or rest pain.[52] However, selective intra-arterial PGI_2 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).[53] In another double-blind trial,[54] PGI_2 administered IV to nondiabetic patients with severe arterial insufficiency produced significantly greater relief (lasting up to 1 month) of rest pain than did placebo, but there was no correlation with changes in ankle-to-brachial pressure index, or ulcer healing.

Beraprost, an orally active PGI_2 analog, was evaluated in the Beraprost et Claudication Intermittente-2 trial[55] of 549 patients with a pain-free walking distance of 50 to 300 m. After 6 months, more patients receiving beraprost (40 μg tid) compared to placebo had an increase in walking distance on a treadmill (44% vs 33%), and pain-free walking distances (82% vs 53%), and maximum walking distances (60% vs 35%). These benefits were modest and probably not clinically significant. The incidence of cardiac death, MI, coronary revascularization, stroke, transient ischemic attack (TIA), or leg ischemia requiring intervention was similar in both groups.

Recommendation

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

Underlying values and preferences: The recommendation places a low value on achieving small gains in walking distance in the absence of demonstrated improvement in quality of life.

1.1.7 Other agents

Other agents with putative antithrombotic activity that have been subjected to RCTs but were found to be ineffective in the treatment of intermittent claudication include the following: the antiserotonin agent ketanserin,[56] suloctidil,[57] fish oil supplementation,[58] and naftidrofuryl.[59–60] Other ineffective drugs for intermittent claudication (such as nifedipine, l-carnitine, etc) are not discussed, as there is little evidence for the role as antithrombotic agents.

Picotamide, an antiplatelet agent that inhibits thromboxane-A_2 synthase and antagonizes thromboxane-A_2 receptors, has been evaluated in one, small, blinded RCT[61] in patients with PAOD. Treatment with picotamide significantly reduced the overall incidence of major and minor cardiovascular events. In a blinded, placebo-controlled RCT,[62] patients treated with picotamide showed no progression of carotid atherosclerosis (as measured by B-mode ultrasound) compared with placebo-treated control subjects. There are no data on whether this agent is superior or equivalent to aspirin or other agents.[63] "Hemodilution therapy" for reducing the plasma viscosity involves the removal of blood and replacing it with a colloidal solution such as hydroxyethyl starch or a low molecular weight dextran one or twice weekly for several weeks, resulting in small improvement in pain-free walking distance in two studies.[64,65]

A Cochrane review[66] assessed the effects of anticoagulant drugs (unfractionated heparin [UFH], low molecular weight heparin [LMWH], and vitamin K antagonists [VKAs]) in patients with PAOD. End points included walking capacity (pain-free walking distance or absolute walking distance), mortality, cardiovascular events, ankle/brachial pressure index, progression to surgery, amputation-free survival, and side effects. 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. 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 VKAs compared to control, with a nonsignificant 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. In conclusion, no benefit of UFH, LMWH, or VKA has been established for intermittent claudication. An increased risk of major bleeding events has been observed especially with VKAs. The Cochrane review[66] concluded that the use of anticoagulants for intermittent claudication cannot be recommended.

Recommendation

1.1.7. In patients with intermittent claudication, we recommend **against** the use of anticoagulants (**Grade 1A**).

2.0 Acute Limb Ischemia

The major causes of acute arterial insufficiency are arterial thrombosis, embolus, and trauma. Extreme vasospasm (*eg*, ergot induced) and arterial dissection are unusual causes. Most traumatic occlusive events are associated with transection, laceration, or occlusion from external compression such as a fracture or dislocation; but in some instances, thrombosis occurs from blunt trauma. Iatrogenic vascular trauma, most often from diagnostic and therapeutic catheter placement, is a common cause of acute arterial occlusion. In most patients early surgery is required, with appropriate repair of the injured vessel. If thrombosis occurred, use of the Fogarty balloon catheter to remove thrombi is often required and is usually effective. Anticoagulation with UFH is variably used at the time of operation, but may be contraindicated because of other injuries. Outcome is related to the seriousness of associated injuries and duration of ischemia; successful vascular repair can be achieved in most cases.

Nontraumatic acute occlusion is mainly 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, paradoxic 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.[67,68]

Thrombotic occlusions of arteries are usually associated with advanced atherosclerosis, and arteries often have preexisting and developed collateral blood supply. For this reason, final occlusion may not be a dramatic event and is sometimes silent; it is not an emergent process in many patients. Thrombosis also occurs in vascular grafts and with other degenerative or inflammatory diseases or with trauma. 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 will depend 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 and was recently reviewed.[69,70] No randomized comparison between the different options is available. Traditionally, thromboembolism in a severely diseased artery or in a vascular graft causing acute ischemia symptoms has been the domain of the vascular surgeon as well, but optimal management needs to be determined.

2.1 Heparin

Patients presenting with acute limb ischemia secondary to thromboembolic arterial occlusion usually receive prompt anticoagulation with therapeutic dosages of UFH 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 (UFH followed by VKA) 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 treatment with immediate systemic anticoagulation with UFH to prevent thrombotic propagation (**Grade 1C**). We also recommend systemic anticoagulation with UFH followed by long-term VKA to prevent recurrent embolism in patients undergoing embolectomy (**Grade 1C**).

2.2 Thrombolysis

Initial intervention with thrombolysis with the aim of eliminating 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 was used in the 1960s and 1970s and 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. Several infusion methods can be used. 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). Dosages schemes vary considerably; an overview of reported dosages was published in a recent consensus document.[71] rt-PA was mainly used in Europe, but since the suspension of urokinase sales in 1998, it has been administered in the United States as well. In addition, new agents are being investigated. For instance, reteplase, a nonglycosylated mutant of alteplase, was tested in a few small series:[72,73] doses of 0.5 up to 2 U/h produced thrombus dissolution rates and bleeding rates that appear comparable to published data with other thrombolytic agents, but a direct comparison is not available.

A new approach is the use of the platelet glycoprotein IIb-IIIa antagonist abciximab as adjuvant therapy to thrombolysis with the hope of improving lytic efficacy and clinical outcome. A pilot trial[74] randomized 70 patients to urokinase plus abciximab or to urokinase plus placebo. At 90 days, amputation-free survival was 96% in the urokinase-abciximab group vs 80% in the urokinase-placebo group. Thrombolysis occurred faster in the former group, but the rate of nonfatal major bleeding was also higher.[74]

Only a few randomized studies compared thrombolytic agents directly. An open trial[75] compared intra-arterial streptokinase to intra-arterial and IV rt-PA in 60 patients with recent onset or deterioration of limb ischemia; initial angiographic success was superior with intra-arterial rt-PA (100%) than with intra-arterial 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. Another randomized trial[76] in 32 patients 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. The Surgery vs Thrombolysis for Ischemia of the Lower Extremity (STILE) study[77] included a comparison of rt-PA and urokinase; patients assigned to thrombolytic treatment received at random one of the two drugs, and the main report mentions similar efficacy and safety for both agents.

A German study[78] 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. The Prourokinase Versus Urokinase for Recanalization of Peripheral Occlusions, Safety and Efficacy trial[79] compared three doses of recombinant prourokinase 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. In assessing all of these data, there is at present no convincing scientific proof 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.[77,80,81,84,85] Two meta-analyses[86,87] are available and 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.

In a small trial,[80] surgical thrombectomy was compared to an intra-arterial continuous infusion of 30 mg of alteplase over 3 h in 20 patients with acute (> 24 h but < 14 days) arterial occlusion and severe leg ischemia. Only patients with a need for intervention were included. Considerable lysis was obtained in six of nine patients treated with alteplase, and half of them subsequently underwent percutaneous transluminal angioplasty. Two early reocclusions occurred. Thrombectomy also resulted in an immediate restitution of blood flow in six of nine cases.

Ouriel et al[81] compared initial thrombolysis complemented with percutaneous transluminal angioplasty or/and surgery vs immediate surgery in 114 patients with limb-threatening ischemia of < 7 days in duration, due to native artery or graft occlusion. Thrombolysis resulted in dissolution of 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[77] 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 intra-arterial catheter-directed thrombolysis with rt-PA or urokinase. 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 duration of 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).[77]

Two additional publications[82,83] analyzed the STILE trial on an intention-to-treat basis for the 30-day, 6-month, and 1-year results in patients with native artery and graft occlusion separately. For 237 patients with native artery occlusion, the composite clinical outcome was in favor of surgery because of a lower incidence of major amputation (0% vs 10% at 1 year, $p = 0.0024$) and recurrent ischemia (35% vs 64% at 1 year, $p < 0.0001$). Factors predictive of a poor outcome with lysis were femoropopliteal occlusion,

diabetes, and critical ischemia. Only 20% of those patients had an onset or progression of ischemic symptoms of < 14 days in duration; in these patients, the 1-year death/amputation rate was similar for surgery and thrombolysis. Overall, lysis failed to reestablish patency in 45% of patients, but 22% did not receive a lytic agent because of problems with catheter positioning.[82] For 124 patients with bypass graft occlusion, there was also a better overall composite clinical outcome at 30 days and 1 year in the surgical group compared to lysis, predominantly due to a reduction in ongoing/recurrent ischemia. However, 39% randomized to lysis failed catheter placement and required surgery. Following successful catheter placement, patency was reestablished by lysis in 84%. A poststudy analysis indicated that limb loss at 1 year was significantly lower in patients with ischemia for < 14 days if treated with thrombolysis compared with those treated surgically (20% vs 48%; $p = 0.026$).[83]

The Thrombolysis or Peripheral Arterial Surgery (TOPAS)[84,85] investigators prospectively compared recombinant urokinase vs surgery in acute arterial occlusion (≤ 14 days). In a first dose-ranging trial,[84] they evaluated the safety and efficacy of three doses of recombinant urokinase in comparison with surgery in 213 patients. The amputation-free survival rate at 1 year was 75% in 52 patients treated initially with recombinant urokinase at 4,000 IU/min, and 65% in 58 surgically treated patients, a nonsignificant difference. The 4,000 IU/min dosage appeared the most appropriate thrombolytic regimen (compared with 2,000 IU/min and 6,000 IU/min) for the first 4 h because it maximized lytic efficacy against the bleeding risk. This optimal dosage regimen (4,000 IU/min for the initial 4 h followed by 2,000 IU/min for up to 48 h) was next tested in a large multicenter trial[85] on 544 patients. Amputation-free survival rates in the urokinase group were 71.8% at 6 months and 65.0% at 1 year, as compared with respective rates of 74.8% and 69.9% in the surgery group; these differences between the two groups 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 which of the two treatments (thrombolysis or surgical intervention) to prefer. They selected heterogeneous patient populations and studied complicated endpoints. The risk of intracranial bleeding remains a major burden for thrombolytic treatment in acute limb ischemia; in three American prospective randomized studies that compared thrombolysis to surgery, the intracranial bleeding rate with thrombolysis was 1.2% (STILE),[77] 2.1% (TOPAS-I),[84] and 1.6% (TOPAS-II).[85]

A working party reached a consensus proposal on the use of thrombolysis in the management of lower-limb arterial occlusion.[71] In native artery occlusion, a management strategy incorporating thrombolysis followed by correction of the causative lesion was proposed as an appropriate strategy in patients with ischemia of < 14 days in duration. Immediate surgical revascularization is to be preferred if thrombolysis would lead to an unacceptable delay in effective reperfusion. In patients with irreversible ischemia, primary amputation is indicated. For occluded bypass grafts, the therapeutic options are either surgical revision and thrombectomy, catheter-directed thrombolysis, or insertion of a new 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 (± 20%), and the question is whether the ultimate yield justifies the labor-intensive and expensive lytic procedure.[88]

Recommendation

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

Underlying 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 Grafts

The superior patency of vein grafts is supported primarily by a single, multicenter, randomized trial published in 1986,[89] which compared saphenous vein grafts with expanded polytetrafluoroethylene prostheses for lower-extremity arterial reconstructions. The primary patency rate at 4 years for infrapopliteal bypasses with saphenous vein was 49%, significantly better than the 12% patency rate with polytetrafluoroethylene bypasses ($p < 0.001$). Although demonstrating clear differences between vein and prosthetic bypasses, this trial is also notable because it documented that even expert surgeons had failure rates that were alarmingly high. Other studies[90,91] show improved patency rates, with no major differences between reversed and nonreversed *in situ* vein grafts in which the valves are rendered incompetent. In the absence of venous conduits, placement of arterial prostheses may be necessary, and most randomized trials evaluating available materials indicate that human umbilical vein grafts have slightly better patency than polytetrafluoroethylene.[92–94] The variable patency of all lower-extremity arterial bypasses, regardless of the type of bypass conduit, suggests the need for adjunctive antithrombotic therapy.

There are similarities and differences in the pathophysiology of thrombotic occlusion of vein grafts and arterial prostheses.[95] Both 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.[95,96] Vascular prostheses, in contrast, are subject to the development of neointimal hyperplasia at anastomoses in which the process stems from the adjacent artery. Patency of vein grafts and vascular prostheses is also adversely affected by progressive inflow and outflow atherosclerosis that reduces flow through the conduit.

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 that rarely develop a complete endothelial lining. Vein grafts may lose variable amounts of their endothelial lining during harvesting and implantation, which may contribute to early occlusion. This suggests the rationale for early antithrombotic therapy that could be discontinued after healing at anastomotic sites and repavement of the graft with endothelium. Arterial prostheses, however, are highly thrombogenic at the time of implantation and remain so. Studies[97,98] with ^{111}In-labeled platelets in humans demonstrate marked uptake of labeled platelets on femoropopliteal bypass prostheses of Dacron or polytetrafluoroethylene, but little or no uptake on vein bypasses in the same position.

3.1 Intraoperative anticoagulation during vascular reconstructions

IV UFH is traditionally administered 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.[99] In the absence of direct monitoring, a fairly intense level of anticoagulation is generally recommended during surgery, because of the wide variability in 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, in which some surgeons do not consider UFH essential, anticoagulation may prevent remote thromboses. In an RCT[100] 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 either group. However, those treated with UFH sustained fewer fatal (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.

Controversy also exists as to whether protamine is beneficial or safe for restoring hemostatic competence after routine peripheral vascular surgery. Protamine commonly causes adverse hemodynamic effects; in diabetics receiving neutral protamine Hagedorn insulin, anaphylactic reactions may occur in 0.6 to 3.0% of patients.[101–103] Reversal of UFH with protamine may not necessarily reduce postoperative bleeding. In a single-center, randomized, double-blind study[104] 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[104] used a dose of UFH (90 U/kg) that is lower than that suggested above, albeit with satisfactory results. Also, rapid reversal of UFH anticoagulation with protamine may increase the risk of thrombosis, at least in carotid endarterectomy. In a small trial[105] of 64 patients randomized to receive protamine or no reversal, the amount of wound drainage was significantly less, and neck swelling was the same. 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 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 UFH at the time of application of vascular cross-clamps (**Grade 1A**).

3.2 Prolonging the patency of grafts

3.2.1 Antiplatelet agents

In 1975, the first RCT[106] showed the protective action of aspirin on thromboembolic events in patients after peripheral bypass surgery. Six trials of antiplatelet therapy in patients with peripheral bypass grafts were described in the Sixth ACCP Consensus Conference on Antithrombotic Therapy.[107] These trials and others were pooled in the second part of the metaanalysis by the 1994 Antiplatelet Trialists' Collaboration.[108] 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 studies, a significant risk reduction of graft occlusion of 32% in patients who received platelet inhibitors was demonstrated.[108]

A metaanalysis[109] performed in 1999 of trials in infrainguinal bypass surgery found five trials[110–114] comparing aspirin (alone or combined with other antiplatelet therapy) against placebo. In 423 patients treated with antiplatelet drugs, 120 bypasses occluded (28.4%), compared with 144 occlusions in 393 randomized control subjects (36.6%).[109] The relative risk was 0.78 (95% confidence interval [CI], 0.64 to 0.95), with a proportional risk reduction of 22%. This corresponds with an absolute risk reduction of 8.2%.

Antiplatelet therapy affects prosthetic and vein grafts differently. A favorable effect of antiplatelet therapy was

demonstrated in the trials[111–113] studying patients with prosthetic grafts, whereas trials[110,114] in which at least 70% had venous grafts were inconclusive. This stronger beneficial effect of aspirin on prosthetic grafts was also supported in a short-term (6 weeks) trial by Clyne et al,[115] who demonstrated a benefit of aspirin and dipyridamole 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 was confirmed in a recent overview analysis.[116] In the Antiplatelet Trialists' Collaboration overview[108] of all antiplatelet studies, neither direct nor indirect comparisons of the effects of different regimens (aspirin, dipyridamole, sulfinpyrazone, ticlopidine and suloctidil) on vascular patency provided convincing evidence that one antiplatelet regimen was more effective than another. In the Dutch Bypass, Oral Anticoagulants or Aspirin (BOA) study[117] (see below), which randomized a large number of patients undergoing lower-extremity bypass (vein and prosthetic) to VKA vs aspirin, aspirin was found to significantly improve patency of prosthetic grafts.

Ticlopidine, an inhibitor of adenosine diphosphate-induced platelet activation, has also been shown to be effective in improving the patency of femoropopliteal and femorotibial bypasses. In a randomized, multicenter, placebo-controlled trial[118] of 243 patients, primary patency at 24 months was 82% in the ticlopidine group and 63% in the placebo group ($p = 0.002$). In clinical use, ticlopidine has now been superceded 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.

Controversy still remains as to whether antiplatelet therapy is best started preoperatively or postoperatively, although the weight of evidence suggests inhibition of platelet function is best established prior to the vascular injury. Two of three trials[112,113] of aspirin showed a benefit in graft patency when the drug was started preoperatively, and the third trial[114] showed no benefit when antiplatelet therapy was begun postoperatively. This third trial[114] had the largest percentage of vein grafts, which are thought to be less thrombogenic. Data from the literature[119–122] on the patency of aortocoronary saphenous vein grafts supports the concept of beginning antiplatelet therapy prior to surgery.

Recommendation

3.2.1. In patients undergoing prosthetic infrainguinal bypass, we recommend aspirin (**Grade 1A**).

3.2.2 VKAs

Two randomized trials[123,124] have compared the efficacy of VKAs to no antithrombotic therapy in patients after infrainguinal bypass surgery. Kretschmer and colleagues[123] studied the effect of long-term treatment with VKA (target international normalized ratio [INR], 2.4 to 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 occluded (19.7%), compared with 23 occlusions in 64 control subjects (35.9%), a relative risk of 0.55 (95% CI, 0.30 to 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%) than in the control group (20.3%). Among the anticoagulated patients, 27 patients (40.9%) died during 10 years of follow-up, compared with 37 subjects (57.8%) in the control group (relative risk, 0.71; 95% CI, 0.49 to 1.01), with an absolute risk reduction of 16.9%. The study reported one fatal GI hemorrhage in the treated group.

A second trial[124] included a more heterogeneous group of 116 patients undergoing various vascular reconstructions (*ie*, vein or prosthetic bypass and endarterectomy). Intention-to-treat analysis showed no difference in patency rate, limb salvage, and survival at the first, second, and third year of follow-up between the anticoagulated group and the control group. These conflicting results with the trial by Kretschmer et al[123] may have been due to the lower level of anticoagulation (target INR, 1.8 to 2.8) in the latter trial, and by 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.

Four trials[117,125–127] comparing VKA with aspirin in patients after infrainguinal bypass surgery or thromboendarterectomy have been reported. In 1979, Schneider et al[125] 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. However, subgroup analysis of patients after vein bypass surgery demonstrated a better patency rate in the group treated with VKAs 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 study randomized a total of 2,690 patients from 80 centers to VKA therapy (target INR, 3 to 4.5) or aspirin, 80 mg/d.[117] All patients in the BOA study 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 occlusions in the aspirin group (hazard ratio, 0.95; 95 CI, 0.82 to 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 to 1.16), and femorocrural bypass grafts (hazard ratio, 0.95; 95% CI 0.70 to 1.30). However, analysis stratified for graft material showed a lower risk of vein graft occlusion in anticoagulated patients than in those receiving aspirin (hazard ratio, 0.69; 95% CI, 0.54 to 0.88). Seventeen patients would require treatment to prevent one occlusion. Conversely, the risk of prosthetic graft occlusion was lower in patients treated with aspirin (hazard ratio, 1.26; 95% CI, 1.03 to 1.55). Fifteen patients

would require treatment to prevent one occlusion. The composite outcome event of vascular death, myocardial infarction, 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 to 1.06). Patients treated with VKA had significantly more major bleeding episodes than patients treated with aspirin: 108 episodes vs 56 episodes (hazard ratio, 1.96; 95% CI, 1.42 to 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 to 4.[128]

Only one trial[129] has directly compared a LMWH with platelet inhibitors to prevent graft thrombosis. Two hundred patients with prosthetic and vein infrainguinal bypass grafts were treated for 3 months with dalteparine compared to aspirin plus dipyridamole. Randomization was stratified according to indication for surgery. Graft patency after 1 year of follow-up was better in the dalteparine group (79.5%) than in the antiplatelet group (64.1%). The subgroup operated on for limb salvage accounted for most of this benefit. Unfortunately, the proportion of patients in this subgroup with prosthetic or vein grafts was not reported.

Recommendation

3.2.2. We suggest that VKA **not** be used routinely in patients undergoing infrainguinal femoropopliteal or distal vein bypass (**Grade 2A**).

Underlying values and preferences: This recommendation attributes relatively little value to small increases in long-term patency and relatively high value to avoiding hemorrhagic complications.

3.2.3 VKA plus aspirin

In a small trial, Sarac et al[126] studied 56 patients with vein bypasses considered to be at high risk for thrombosis due to suboptimal venous conduit, poor runoff, or reoperative grafting. All patients received preoperative aspirin. One group was treated with IV UFH immediately postoperatively (target activated partial thromboplastin time, 1.5 times control), until long-term treatment with VKA (target INR, 2 to 3) and aspirin were instituted. The other group received aspirin, 325 mg/d. The cumulative 3-year primary rates were significantly greater in the UFH, VKA, and aspirin group 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%).

In the Veterans Affairs trial,[127] 831 patients with vein and prosthetic bypasses were stratified for vein and prosthetic grafts and randomized to treatment with low-intensity VKA (INR, 1.4 to 2.8) plus aspirin, 325 mg/d, or aspirin alone. The average follow-up was 39.3 months in the vein bypass group and 36.6 months in the group receiving prosthetic grafts. 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 to 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. In patients with prosthetic bypasses, 44 occlusions (23.5%) occurred in 187 patients with VKA plus aspirin, vs 64 occlusions (34.4%) in patients treated with aspirin (risk ratio, 0.62; 95% CI, 0.42 to 0.92), resulting in a 38% proportional risk reduction with combination treatment. This effect was due to the difference found in the 212 patients with 6-mm bypasses (mainly femoropopliteal above knee). 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 to 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.

Recommendation

3.2.3. For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, we recommend **against** VKA plus aspirin (**Grade 1A**). For those at high risk of bypass occlusion and limb loss, we suggest VKA plus aspirin (**Grade 2B**).

Underlying values and preferences: These recommendations place a high value on the avoidance of bleeding complications but recognize that there are circumstances in which the threat of limb loss and major disability may supercede this risk.

4.0 Carotid Endarterectomy

4.1 Aspirin

In patients undergoing carotid endarterectomy, aspirin therapy is an important adjunct. 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 ^{111}In-labeled platelets document marked deposition of platelets at the endarterectomy site immediately after operation.[130,131] The intensity of platelet accumulation decreases over time, possibly because of re-endothelialization of the endarterectomy site. In one study[131] of 22 patients, treatment of patients undergoing carotid endarterectomy with aspirin plus dipyridamole significantly decreased ^{111}In platelet deposition, and appeared to decrease the incidence of perioperative stroke. A study[132] of 125 patients assessing the benefit of aspirin therapy for longer periods after carotid endarterectomy has been reported. Patients receiving aspirin, 650 mg bid, started on the fifth postoperative day had a slight but significant reduction in unfavorable end points 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 very-low-dose aspirin therapy, 50–100 mg/d, with placebo after carotid endarterectomy.[133] Therapy was started 1 week to 3 months after operation, and no significant benefit of very-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[134] of aspirin, 75 mg/d, vs placebo in 232 patients; therapy was started preoperatively and was associated with a marked reduction in intraoperative and postoperative stroke.

The ASA and Carotid Endarterectomy Trial[135] was a multicenter, randomized, double-blind 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). 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 receiving 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 receiving < 650 mg of aspirin and who were randomized ≥ 2 days before surgery. In the efficacy analysis, there were 566 patients in the low-dose group, and 550 patients 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%, $p = 0.002$; 4.2% vs 10.0%, $p = 0.0002$).[135]

Based on these considerations, perioperative aspirin therapy, 75 to 325 mg/d, is appropriate therapy 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 incomplete reversal with protamine of intraoperative UFH, hypertension, and perioperative antiplatelet therapy.[136,137] 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

4.1. We recommend that aspirin, 75 to 325 mg, be given preoperatively and continued indefinitely in patients undergoing carotid endarterectomy (**Grade 1A**).

5.0 Asymptomatic and Recurrent 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[138,139] suggests that aspirin may be beneficial in patients with advanced stenosis who do not undergo carotid endarterectomy. 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.[140] 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.

Significant stenoses recurring at the site of endarterectomy are found in as many as 10 to 19% of patients after carotid endarterectomy.[141] Data from retrospective studies[142,143] suggest that antiplatelet therapy does not reduce the incidence of recurrent carotid artery stenosis. A randomized trial[144] confirmed that treatment with aspirin and dipyridamole does not prevent symptomatic or asymptomatic recurrent stenosis after carotid endarterectomy. Although there are no data to recommend aspirin treatment for patients with asymptomatic or recurrent carotid stenosis in order to prevent progression or symptom development, these patients have a high prevalence of associated coronary and PAOD. Therefore, antiplatelet therapy may improve long-term cardiovascular outcomes.

Recommendation

5.0. In nonoperative patients with asymptomatic or recurrent carotid stenosis, we recommend lifelong aspirin, 75 to 162 mg/d (**Grade 1C+**).

6.0 Lower-Extremity Endovascular Procedures

Recommendations for optimal antithrombotic therapy for lower-extremity arterial balloon angioplasty are hampered by the lack of agreement over the proper role of these endovascular procedures, and a lack of data from suitable RCTs. 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.[145] There is less agreement regarding the suitability of transluminal angioplasty for more diffuse and extensive patterns of occlusive disease.

Complicating the matter even further is the technologic "moving target" of catheter-based interventions. The use of self-expanding metallic stents can salvage what otherwise might be an unacceptable technical outcome from

balloon angioplasty alone. The routine use of stents, however, has not been shown to improve the results of lower extremity balloon angioplasty.[145,146] Newer devices such as medication-coated stents are being tested in the lower-extremity arterial circulation.[147] Based on the promising early results seen with coronary stenting,[148] such devices might find a role in the peripheral arterial vascular bed. It cannot be assumed then, that results from clinical trials evaluating antithrombotic therapy for balloon angioplasty alone will necessarily extrapolate to its use with existing and newer stent devices.

Life-long antiplatelet therapy is recommended for all patients with PAOD on the basis of their increased risk of coronary and cerebrovascular events. Given this, the primary issue governing the proper use of antithrombotic therapy in conjunction with lower-extremity balloon angioplasty and stenting is that of agent and dosage.

Whether antiplatelet therapy improves patency of lower-extremity angioplasty is a separate question, and has been addressed in two RCTs[149,150] comparing combinations of aspirin and dipyridamole with placebo. In a single-center trial[149] 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 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[150] 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). Primary patency and overall 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 commonly done now in clinical practice with the advent of low-profile, self-expanding, flexible stents.

It is not uncommon for combinations of anticoagulation and antiplatelet therapy to be used in patients undergoing femoropopliteal, and tibial artery balloon angioplasty. This does not appear to be supported by the results of the three RCTs[151–153] published regarding this issue; a total of 438 patients were randomized in the three studies. In all three studies,[151–153] the arterial patency rates were slightly lower in the anticoagulation groups, but this was not statistically significant in any of the studies. Also, there tended to be more bleeding complications in the anticoagulation groups, including one fatal intracerebral hemorrhage.

Combinations of thienopyridines (ticlopidine, clopidogrel) with aspirin are also used in clinical practice as antithrombotic therapy for lower-extremity balloon angioplasty and stenting, particularly when the treated arteries are in the femoropopliteal segments, and in the smaller-diameter tibial arteries. As yet, such combinations have not been studied in RCTs. Interest in the use of aspirin with either ticlopidine or clopidogrel has undoubtedly been stimulated by the favorable results reported with aspirin and ticlopidine in comparison with aspirin alone and aspirin with warfarin after coronary artery stenting.[154] There are important differences between lower-extremity arterial interventions and those in the coronary circulation to call into question the validity of such an extrapolation. Nonetheless, given the relatively high rate of failure of lower-extremity intervention and the increasing use of stents in these interventions, investigation aimed at studying such combinations of antiplatelet therapy in this setting is needed.

In summary, antiplatelet therapy with aspirin is indicated for all patients undergoing lower-extremity balloon angioplasty (with or without stenting), as it is currently recommended for all patients with PAOD. 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 or tibial arterial angioplasty and stenting. Specifically, the addition of anticoagulation to antiplatelet therapy does not appear to convey any advantage, and likely increases the risk of bleeding complications. Based on the data from the coronary circulation, it is reasonable to consider combinations of aspirin and thienopyridines in high-risk, small-diameter tibial artery angioplasty.

Recommendation

6.0. For all patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin, 75 to 162 mg/d (**Grade 1C+**).

Summary of Recommendations

1.0 Chronic Limb Ischemia

1.1 Antiplatelet therapy

1.1.1 Aspirin

1.1.1. We recommend lifelong aspirin therapy, 75 to 325 mg/d, in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease (**Grade 1A**) and in those without clinically manifest coronary or cerebrovascular disease (**Grade 1C+**).

1.1.2 Ticlopidine

1.1.2. We recommend clopidogrel over ticlopidine (**Grade 1C+**).

1.1.3 Clopidogrel

1.1.3. We recommend clopidogrel in comparison to no antiplatelet therapy (**Grade 1C+**), but suggest that aspirin be used instead of clopidogrel (**Grade 2A**).
Underlying values and preferences: This recommendation

places a relatively high value on avoiding large expenditures to achieve small reductions in vascular events.

1.1.4 Cilostazol

1.1.4. For patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention, we suggest cilostazol (**Grade 2A**). We suggest that clinicians **not** use cilostazol in those with less-disabling claudication (**Grade 2A**).

Underlying values and preferences: The recommendation against cilostazol for those with less-disabling claudication places a relatively low value on small possible improvements in function in the absence of clear improvement in health-related quality of life.

1.1.5 Pentoxifylline

1.1.5. We recommend **against** the use of pentoxifylline (**Grade 1B**).

1.1.6 Prostaglandins

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

Underlying values and preferences: The recommendation places a low value on achieving small gains in walking distance in the absence of demonstrated improvement in quality of life.

1.1.7 Other agents

1.1.7. In patients with intermittent claudication, we recommend **against** the use of anticoagulants (**Grade 1A**).

2.0 Acute Limb Ischemia

2.1 Heparin

2.1. In patients with acute arterial emboli or thrombosis, we recommend treatment with immediate systemic anticoagulation with UFH to prevent thrombotic propagation (**Grade 1C**). We also recommend systemic anticoagulation with UFH followed by long-term VKA to prevent recurrent embolism in patients undergoing embolectomy (**Grade 1C**).

2.2 Thrombolysis

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

Underlying 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 Grafts

3.1 Intraoperative anticoagulation during vascular reconstructions

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

3.2 Prolonging the patency of grafts

3.2.1 Antiplatelet agents

3.2.1. In patients undergoing prosthetic infrainguinal bypass, we recommend aspirin (**Grade 1A**).

3.2.2 Vitamin K antagonists

3.2.2. We suggest that VKA **not** be used routinely in patients undergoing infrainguinal femoropopliteal or distal vein bypass (**Grade 2A**).

Underlying values and preferences: This recommendation attributes relatively little value to small increases in long-term patency and relatively high value to avoiding hemorrhagic complications.

3.2.3 VKA plus aspirin

3.2.3. For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, we recommend **against** VKA plus aspirin (**Grade 1A**). For those at high risk of bypass occlusion and limb loss, we suggest VKA plus aspirin (**Grade 2B**).

Underlying values and preferences: These recommendations place high value on the avoidance of bleeding complications but recognize that there are circumstances where the threat of limb loss and major disability may supercede this risk.

4.0 Carotid Endarterectomy

4.1 Aspirin

4.1. We recommend that aspirin, 75 to 325 mg/d, be given preoperatively and continued indefinitely in patients undergoing carotid endarterectomy (**Grade 1A**).

5.0 Asymptomatic and Recurrent Carotid Stenosis

5.0. In nonoperative patients with asymptomatic or recurrent carotid stenosis, we recommend lifelong aspirin, 75 to 162 mg/d (**Grade 1C+**).

6.0 Lower Extremity Endovascular Procedures

6.0. For all patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin, 75 to 162 mg/d (**Grade 1C+**).

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