

# Antithrombotic Therapy in Peripheral Arterial Occlusive Disease

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**Abbreviations:** ACD = absolute claudication distance; CI = confidence interval; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NASCET = North American Symptomatic Carotid Endarterectomy Trial; PGE<sub>1</sub> = prostaglandin E<sub>1</sub>; PGI<sub>2</sub> = prostaglandin I<sub>2</sub>; PTFE = polytetrafluoroethylene; rtPA = recombinant tissue plasminogen activator; tPA = tissue plasminogen activator; UFH = unfractionated heparin

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**A**therosclerosis is the cause of the vast majority of cases of chronic peripheral arterial occlusive disease. The arteries most frequently involved, in order of occurrence, are the femoropopliteal-tibial, aortoiliac, carotid and vertebral, splanchnic and renal, and brachiocephalic. Fibromuscular dysplasia, inflammatory arteritides, and congenital arterial malformations are much rarer causes of arterial insufficiency. The causes of acute arterial occlusion are embolism, thrombosis, and trauma. The goals of therapy in chronic arterial occlusive disease are to relieve ischemic symptoms (intermittent claudication and rest pain), to alleviate disability, and to prevent progression that might lead to gangrene and limb loss. The objectives of therapy in acute arterial occlusion are to restore blood flow and to preserve life and limb. Antithrombotic therapy is a rational consideration in patients with peripheral arterial occlusive disease. In chronic disease, antithrombotic therapy is designed to prevent progression and thrombotic occlusion or to prevent thrombotic complications after vascular reconstructions and other interventions. In acute arterial occlusion from embolism or thrombosis, effective anticoagulant therapy will prevent propagation of thrombi into proximal and distal arterial branches with attendant compromise of collateral flow; may prevent reocclusion after surgical or interventional procedures to reestablish flow; or, in the case of embolism, may prevent recurrence. The antithrombotic agents available are anticoagulants, antiplatelet agents, thrombolytic drugs, and dextran (Table 1).

## CHRONIC EXTREMITY ARTERIAL INSUFFICIENCY

Epidemiologic studies have documented that 2 to 3% of men and 1 to 2% of women  $\geq 60$  years of age have intermittent claudication.<sup>1-3</sup> The prevalence, however, is threefold to fourfold higher when sensitive noninvasive tests are applied to the limbs of asymptomatic as well as symptomatic individuals.<sup>4,5</sup> The prevalence also increases with age. The natural course of chronic lower-extremity arterial insufficiency is that after 5 to 10 years, the conditions of approximately 70 to 80% of patients remain unchanged or improved, 20 to 30% have progression of symptoms and require intervention, and  $< 10\%$  require

amputation.<sup>6-8</sup> 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.<sup>8</sup>

Despite the rather benign prognosis for the limb, intermittent claudication may be viewed as an ominous sign of underlying disseminated atherosclerosis, and afflicted individuals have a twofold to threefold increase in cardiovascular mortality on long-term follow-up in comparison with age-matched control subjects.<sup>1,2,9,10</sup> The prognosis for limb and life is worse for more severely affected individuals.<sup>7,9</sup> The excessive mortality rate is related to stroke and myocardial infarction (MI), because carotid atherosclerosis and ischemic heart disease are common in patients with lower-extremity arterial disease.<sup>10</sup> There is an inverse relationship between the ankle-to-brachial pressure index and clinically manifest cardiovascular disease and risk factors.<sup>5</sup> The lower the index, the greater the occurrence of adverse cardiac events, strokes, and cardiovascular deaths. Even patients with modest, asymptomatic reductions in the ankle-to-brachial pressure index (0.8 to 1.0) are at increased risk of developing clinically manifest cardiovascular disease. These findings lead to the conclusion that leg artery disease should be regarded not only as a marker of generalized atherosclerosis but also as an indicator associated with an increased risk of premature death.<sup>10</sup>

## Aspirin

Aspirin therapy may modify the natural history of chronic lower-extremity arterial insufficiency as well as lower the incidence of associated cardiovascular events. Data from one randomized clinical trial suggest that aspirin, alone or combined with dipyridamole, will delay the progression of established arterial occlusive disease as assessed by serial angiography<sup>11</sup> and decrease the need for arterial reconstruction when used for primary prevention of adverse cardiovascular events in men.<sup>12</sup> The beneficial effect of aspirin is most likely related to prevention or retardation of platelet thrombogenesis on the surface of atherosclerotic plaques; experimental and clinical trials have suggested that aspirin has no effect on the enlargement of plaques.<sup>13</sup> Although a few reports<sup>14-18</sup> suggest beneficial effects of anticoagulants and antiplatelet agents in patients with peripheral vascular disease, no convincing data from properly designed large trials demonstrate that antithrombotic therapy will delay or prevent progression of atherosclerosis.

Ticlopidine has also been evaluated in patients with intermittent claudication. Reports from Europe have shown a beneficial effect of ticlopidine for relieving symptoms, increasing walking distance, and improving lower-extremity ankle pressure indexes.<sup>19,20</sup> In addition, a meta-analysis of these trials 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.<sup>21</sup> In a multicenter, randomized clinical trial, use of ticlopidine (250 mg/d) in patients with claudication was shown to result in a need for fewer vascular surgery procedures

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**Table 1—Summary of Antithrombotic Therapy in Peripheral Vascular Disease**

Clinical Problem	Antithrombotic Therapy	Grade of Recommendation
Chronic lower extremity ischemia	Aspirin (to reduce risk of stroke and MI)	1C
	Clopidogrel	2A
Claudication	Aspirin (to reduce risk of stroke and MI)	1C
	Cilostazol (in addition to aspirin)	2A
Acute arterial occlusion and ischemia	Heparin	1C
	Intra-arterial thrombolytic therapy (tPA)	2B
Intraoperative anticoagulation during vascular surgery	Heparin	1A
Infringuinal vein bypass	Aspirin (to reduce risk of stroke and MI)	1C
	Clopidogrel (unable to take aspirin)	1C
Infringuinal prosthetic bypass	Aspirin (with or without dipyridamole)	1A
Infringuinal bypass at high thrombotic risk	Aspirin and warfarin	1B
Carotid endarterectomy	Aspirin	1A

during a 7-year period than use of a placebo control.<sup>22</sup> The need for subsequent vascular surgery was reduced by about half (relative risk, 0.486;  $p < 0.001$ ). The specific indications for the subsequent vascular procedures were not addressed, nor was the risk of adverse events such as neutropenia. Ticlopidine is associated with adverse hematologic effects generally not associated with aspirin. In addition to neutropenia, thrombotic thrombocytopenic purpura has been reported in 60 patients taking ticlopidine.<sup>23</sup> Although the drug is promising, there is a need for confirmatory studies before ticlopidine can be recommended.

A compelling reason to administer aspirin to patients with peripheral arterial disease is to prevent death and disability from stroke and MI. In the original meta-analysis from the Antiplatelet Trialists Collaboration, 31 randomized trials with > 29,000 patients with vascular disease were analyzed, and the data convincingly showed that long-term aspirin therapy significantly reduced overall vascular mortality, as well as nonfatal stroke and MI.<sup>24</sup> An update of this meta-analysis reviewed 174 randomized trials of antiplatelet therapy involving > 100,000 patients.<sup>25</sup> Among high-risk patients, aspirin therapy was protective, reducing nonfatal MI by one third, nonfatal stroke by one third, and death from all vascular causes by one sixth. The beneficial effect was noted for men and women of all ages and was unrelated to the presence of diabetes and hypertension. Specific subgroup analyses of patients with peripheral arterial insufficiency and infringuinal arterial reconstructions were considered, and both groups benefited from antiplatelet therapy. For all conditions, aspirin at 80 to 325 mg/d was at least as effective as any other regimen, including higher-dose aspirin therapy that is more prone to cause side effects and GI complications.<sup>25</sup> In the appendix of the article, a summary of each of the 174 trials is provided.<sup>25</sup> From this information, it appears that the data supporting the use of antiplatelet therapy in peripheral vascular disease (trials studying intermittent claudication and noncoronary grafting) are primarily based on studies of ticlopidine. However, given the high prevalence of coronary artery disease and cerebrovascular disease, it would seem reasonable to extrapolate outcomes from the other studies to patients with peripheral vascular disease.

### *Clopidogrel*

Clopidogrel is a new thienopyridine, the chemical structure of which is similar to ticlopidine, that exerts an irreversible antiplatelet effect that is primarily directed against adenosine diphosphate–induced stimulation of platelet function.<sup>26</sup> In a multicenter, randomized clinical trial of 19,185 patients, the relative efficacy of clopidogrel was compared with aspirin in reducing the risk of a composite end point of ischemic stroke, MI, or vascular death.<sup>27</sup> The study population comprised patients with recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. The overall incidence of composite end points was lower in the group treated with clopidogrel (5.32% per year) than with aspirin (5.83%;  $p = 0.043$ ). Particularly noteworthy is that subgroup analysis revealed that virtually all of the benefit associated with clopidogrel was observed in the group with symptomatic peripheral vascular disease, who as a group sustained significantly fewer MIs and vascular-related deaths than did the aspirin-treated group. Additional studies, particularly ones that specifically address peripheral vascular disease, are needed to define the role of clopidogrel in the treatment of these patients.

### *Vasodilators*

Prostaglandins with antiplatelet and vasodilatory effects, such as prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>), have been administered IV or intra-arterially to patients with advanced chronic arterial insufficiency in hopes of relieving rest pain and healing ischemic ulcers.<sup>28</sup> PGE<sub>1</sub> was found to be ineffective in a randomized, double-blind, multicenter trial.<sup>29</sup> Selective intra-arterial PGI<sub>2</sub> 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's disease).<sup>30</sup> However, this route of administration is impractical and may cause complications, and these results have not been confirmed in patients suffering from pure atherosclerotic arterial insufficiency. In another double-blind trial, PGI<sub>2</sub> given IV to nondiabetic patients with severe arterial insufficiency produced significantly greater relief of rest pain than did placebo.<sup>31</sup> Relief lasted up to 1 month, was not correlated

with changes in ankle-to-brachial pressure indexes, and was not associated with ulcer healing. PGI<sub>2</sub> administered IV was evaluated in a double-blind trial that contained a high proportion of diabetics, and the results were disappointing in that PGI<sub>2</sub> had no beneficial effect on ulcer healing or rest pain.<sup>32</sup> Thus, it appears that PGI<sub>2</sub> may provide temporary relief of rest pain in nondiabetic patients with severe arterial insufficiency and may promote healing of ischemic ulcers when given intra-arterially. However, it is doubtful that such therapy will ultimately prevent amputation in patients with end-stage, nonreconstructible vascular disease. In a small, randomized open study, PGE<sub>1</sub> 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.<sup>33</sup> In a more recent multicenter, randomized clinical trial studying the effect of PGE<sub>1</sub> for chronic critical ischemia of the leg, 1,560 patients were randomly assigned to receive either a daily IV infusion of PGE<sub>1</sub> or nothing (open-label study) during their hospital stay.<sup>34</sup> A combined end point of death and peripheral and cardiovascular illness was evaluated at hospital discharge and during 6 months of follow-up. At hospital discharge, there was a more modest reduction in composite outcome events in the PGE<sub>1</sub> group than in the control subjects (63.9% vs 73.6%; relative risk, 0.87;  $p < 0.001$ ). This difference was not significant at 6 months (52.6% vs 57.5%; relative risk, 0.92;  $p = 0.074$ ).

AS-013, a PGE<sub>1</sub> prodrug, was evaluated in a randomized clinical trial 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.<sup>35</sup> This difference was statistically significant ( $p < 0.01$ ), although the clinical significance of the increase is somewhat marginal. Two significant complications occurred in patients receiving AS-013: one episode of atrial fibrillation and one episode of sustained hypotension. In current practice, the lack of available oral forms of prostaglandins, their adverse hemodynamic effects, and lack of demonstrated superiority over conventional agents such as aspirin have resulted in a limited use of these compounds.

### PENTOXIFYLLINE

Pentoxifylline, a methylxanthine derivative, is one of two hemorheologic agents currently approved by the Food and Drug Administration for treatment of intermittent claudication. In patients with peripheral arterial disease, pentoxifylline has been reported to improve abnormal erythrocyte deformability,<sup>36,37</sup> reduce blood viscosity,<sup>38</sup> and decrease platelet reactivity and plasma hypercoagulability.<sup>39</sup> Thus, pentoxifylline is a weak antithrombotic agent, and its beneficial effects may stem from other pharmacologic properties. A number of clinical trials have evaluated pentoxifylline. Many concluded that pentoxifylline was significantly more effective than placebo in improving treadmill walking distances,<sup>40-46</sup> but six trials could not demonstrate consistent benefit.<sup>47-52</sup> In most trials, patients treated with placebo also had significant

improvement, and this tended to obscure benefits attributable to active drug treatment. A critical review of these trials concluded that the actual improvement in walking distance attributable to pentoxifylline is often unpredictable, may not be clinically important compared with the effects of placebo, and does not justify the added expense for most patients.<sup>53</sup> The drug may have a role in a few patients with markedly reduced walking distances who are unresponsive to or cannot engage in exercise therapy; for such patients, even a small increase in claudication walking distance may allow activities that were previously impossible.

### CILOSTAZOL

Cilostazol is the newest agent approved by the Food and Drug Administration for the treatment of intermittent claudication. Cilostazol is a type III phosphodiesterase inhibitor and possesses antiplatelet and vasodilating properties. Its mechanism of action as a treatment for claudication is not fully understood. There have been several published clinical trials that have evaluated the efficacy of cilostazol as a therapeutic agent for intermittent claudication.<sup>54-57</sup> In the first of these published trials, 239 patients were randomly assigned to receive a 16-week course of cilostazol or placebo.<sup>54</sup> The primary end point of absolute claudication distance (ACD) increased 47% in the cilostazol group but only 13% in the control subjects ( $p < 0.001$ ). Functional status assessment with the SF-36 and the Walking Impairment Questionnaire showed improvement with cilostazol compared with control subjects. The absolute difference in ACD between the two groups at 16 weeks ranged from only 40 to 50 m. Also, there were significantly more side effects with cilostazol, most notably headache (30%) and diarrhea (12.6%).

In two smaller clinical trials (each  $< 100$  patients), Dawson and colleagues<sup>55,56</sup> evaluated cilostazol in patients with intermittent claudication. In the first of these, 81 patients were randomly assigned to 12 weeks of cilostazol or placebo treatment; 66 patients completed the study. At 12 weeks, the ACD increased 31% with cilostazol, vs a drop of 9% with placebo ( $p < 0.01$ ). The absolute difference in ACD between the two groups was 80 m ( $p = 0.002$ ). In their second study, 45 patients with claudication were randomly assigned to one of three groups, cilostazol, pentoxifylline, or placebo for 24 weeks. To assess the effect of drug treatment withdrawal, at 24 weeks the treatment was changed to placebo for all groups, and follow-up was continued for 6 more weeks. The study showed a more significant decrease in ACD after cessation of cilostazol therapy than with either pentoxifylline or placebo. Although the numbers are too small for meaningful comparison, the increase in ACD from baseline was similar in both the cilostazol and pentoxifylline groups (109% and 94%, respectively).

Beebe and colleagues<sup>57</sup> recently reported the results of a clinical trial of 516 patients randomly assigned to cilostazol or placebo therapy for 24 weeks. There were two cilostazol groups (100 or 50 mg twice daily). The ACD showed significant improvement with cilostazol, particularly for the 100-mg-dose group, in which there was an

absolute difference of > 80 m compared with placebo at 24 weeks. The geometric mean change in ACD from baseline was also significantly greater for cilostazol (100 mg), 1.51 compared with 1.15 for placebo ( $p < 0.001$ ). As in the study by Money and others,<sup>54</sup> there was also a significant improvement in functional outcomes with cilostazol as measured by the SF-36 and the Walking Impairment Questionnaire. Unlike the earlier report, there was no difference in the incidence of adverse events in the three groups.

### Other Agents

Other agents subjected to randomized clinical trials that were found to be ineffective in the treatment of intermittent claudication include the antiserotonin agent ketanserin,<sup>58</sup> suloctidil,<sup>59</sup> nifedipine,<sup>60</sup> fish oil supplementation,<sup>61</sup> naftidrofuryl,<sup>62,63</sup> and ethylenediaminetetraacetic acid chelation therapy.<sup>64,65</sup> A promising drug is L-carnitine, an agent that appears to facilitate the transfer of acylated fatty acids and acetate across mitochondrial membranes, thereby enhancing available energy stores and improving oxidative muscle metabolism. A small, randomized trial demonstrated significant improvements in walking in comparison with placebo.<sup>66</sup> Picotamide, an antiplatelet agent that inhibits thromboxane A<sub>2</sub> synthase and antagonizes thromboxane A<sub>2</sub> receptors, has also been evaluated in a small, double-blind, randomized trial in patients with peripheral arterial occlusive disease.<sup>67</sup> Treatment with picotamide significantly reduced the overall incidence of major and minor cardiovascular events. In a double-blind, placebo-controlled trial, patients treated with picotamide showed no progression of carotid atherosclerosis as measured by B-mode ultrasound compared with placebo-treated control subjects.<sup>68</sup> It is not known whether this agent is superior or equivalent to aspirin.

### ACUTE EXTREMITY ARTERIAL INSUFFICIENCY

The major causes of acute arterial occlusion are trauma, arterial thrombosis, and arterial embolus. Most traumatic occlusive events are associated with transection, laceration, or occlusion from external compression such as from a fracture or dislocation, but in some instances, thrombosis occurs from blunt trauma. Iatrogenic vascular trauma, most often from diagnostic and therapeutic arterial catheter placement, is increasing in frequency and is a common cause of acute arterial occlusion.<sup>69,70</sup> In most cases, early surgery is required, with appropriate repair of the injured vessel. In thrombotic occlusion, use of the Fogarty balloon catheter to remove thrombi is often required and is usually effective. Anticoagulation with heparin 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 is achieved in 90 to 95% of cases.<sup>71</sup>

Nontraumatic acute occlusion may be embolic or thrombotic. Arterial embolism is a common cause of acute arterial occlusion, and, in approximately 85% of cases, the emboli arise from a cardiac source.<sup>72</sup> Cardiac causes include atrial fibrillation associated with valvular heart

disease or mural thrombi in an infarcted left ventricle. Noncardiac causes of emboli include arterial aneurysms; atherosclerotic plaques, especially when ulcerated; recent vascular surgery; paradoxical emboli from venous thrombi in the lower extremities; and, rarely, arteritis or vascular trauma. Approximately two thirds of noncerebral emboli enter vessels of the lower extremity, and 50% of these obstruct the iliofemoral arterial segment; the remainder involve the popliteal and tibial vessels. The upper-extremity and renal plus visceral vessels each receive approximately 15% of emboli.<sup>72,73</sup>

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 most patients. Arterial occlusions most frequently involve the lower extremities. In the upper extremities, arterial occlusions are better tolerated because of rich collateral blood supply, and gangrene or ischemic rest pain is rare in the absence of distal embolization. Some patients with stable intermittent claudication will suddenly develop ischemic rest pain and have barely detectable Doppler arterial signals at the ankle. Many vascular surgeons fully anticoagulate these patients with heparin to prevent occlusion of marginal collateral beds and to prevent tissue necrosis while performing a thorough workup for semiselective vascular reconstruction. It is unknown whether heparin improves outcome in this circumstance.

Introduction of the Fogarty balloon catheter in 1963 dramatically altered the management of peripheral emboli. It reduced mortality from this disorder by nearly 50% and decreased the incidence of amputation by approximately 35%.<sup>72</sup> In nearly all patients, prompt removal of emboli is indicated unless the patient is moribund, the involved extremity is gangrenous, or evidence of ischemia is advanced when the patient is first seen.<sup>74</sup> With this approach, mortality is approximately 15%, and death is usually caused by underlying cardiopulmonary disorders; limb salvage, even in elderly patients, ranges from 62 to 96%.<sup>74,75</sup> Mortality is higher in patients with embolism than in patients with acute arterial thrombosis because severe cardiac disease is more common.<sup>76</sup>

### Heparin

To our knowledge, no studies have established unequivocally a beneficial role of any of the antithrombotic agents in patients with acute embolic occlusion. The value of heparin treatment is uncertain, but most surgeons do administer heparin and continue the treatment throughout the perioperative period.<sup>77-79</sup> If revascularization is delayed after an embolic or thrombotic event, thrombotic propagation from the site of occlusion often develops after a 6- to 8-h period.<sup>80</sup> Heparin treatment may prevent or limit this process. The major role for anticoagulant therapy after embolization, however, is to prevent embolic recurrence. Evidence available from retrospective, nonrandomized studies suggests that anticoagulant therapy with heparin or oral anticoagulants reduces the frequency of recurrence by approximately 75% compared with no

therapy.<sup>72,81</sup> Reduced mortality was also observed after long-term anticoagulant therapy. The adverse effect of perioperative anticoagulant therapy in these studies was a substantially higher incidence of wound complications, particularly hematomas (up to 33%).<sup>81,82</sup> Close monitoring and appropriate control of heparin given continuously after vascular operations can minimize bleeding complications.<sup>83</sup> Others have noted no reductions in recurrent emboli and mortality with postoperative heparin treatment.<sup>84</sup> To determine whether the benefits of postoperative anticoagulant therapy outweigh the risks, a randomized trial is necessary.

### Thrombolysis

Thrombolytic therapy has been evaluated in numerous clinical trials involving patients with thrombotic or embolic occlusions. The initial approach was with systemic therapy using a priming dose of the thrombolytic agent to overcome inhibitors and to achieve an intense thrombolytic state in the circulating blood, which was sustained by constant IV infusion for periods ranging from a few hours to several days. In 10 uncontrolled studies in the early 1970s involving 1,800 patients, partial or substantial lysis was observed in approximately 40%, and no discernible lysis was observed in the remaining 60%.<sup>85</sup> Results were influenced by the duration of occlusion before treatment, with best results within 72 h of onset of symptoms, but much older lesions were shown to undergo lysis in some patients. No apparent difference was observed between the response of embolic or thrombotic lesions or the location of the occlusion or condition of the extremity before treatment was begun.<sup>86</sup> Bleeding complications of serious magnitude were observed in approximately one third of the patients.

In 1974, Dotter et al<sup>87</sup> reported the use of low-dose streptokinase administered locally at the site of the thrombus; they obtained lysis without complication. Since then, efficacy of streptokinase, urokinase, or tissue plasminogen activator (tPA) infused near or into the thrombus has been reported by many investigators.<sup>88-97</sup> Regional or intra-arterial thrombolytic therapy has become the preferred technique among interventional radiologists and vascular surgeons. The rate of successful reperfusion (50 to 85%) appears higher than with systemic thrombolytic therapy, and an important advantage of the selective approach is that it allows simultaneous angiographic definition of the nature of the occlusion (embolic vs thrombotic) and vessel wall abnormalities that would lead to rethrombosis if not corrected by surgery or balloon angioplasty. A major drawback to this approach is that arterial catheterization is required for prolonged periods (hours to days), leading to major bleeding and thromboembolic complications in 6 to 20% of patients.<sup>97,98</sup> Despite this, intra-arterial thrombolytic therapy appears superior to systemic treatment. In a randomized trial comparing intra-arterial tPA, IV tPA, and intra-arterial streptokinase, intra-arterial tPA was significantly more effective in establishing reperfusion and had a lower incidence of hemorrhagic complications.<sup>99</sup> Other studies have documented the superiority of both urokinase and tPA over streptokinase.<sup>100-102</sup>

Randomized trials comparing surgical thrombectomy and thrombolytic therapy in patients with acute arterial ischemia provide helpful information. Single-center, small trials document comparable limb salvage rates with both modes of therapy.<sup>103,104</sup> In one study, patients given thrombolytic therapy had significantly improved 1-year cumulative survival, which appeared to be the result of fewer in-hospital cardiopulmonary complications that were common postoperative events.<sup>104</sup> A larger, multi-center trial compared intra-arterial thrombolytic therapy with urokinase or tPA with surgery in patients presenting with recent-onset lower-limb ischemia caused by nonembolic arterial and bypass graft occlusion.<sup>105</sup> The study was stopped prematurely when an interim analysis demonstrated that patients randomly assigned to surgery did significantly better than those given thrombolytic therapy. However, there appeared to be discordant results depending on the clinical presentation. In patients presenting with ischemic symptoms of > 2 weeks' duration, surgical revascularization was clearly superior; in patients presenting with acute ischemia of < 2 weeks' duration, amputation rates were lower with thrombolytic therapy. However, this latter finding stemmed from *post hoc*, subgroup analysis and cannot be considered definitive. There was no difference in efficacy or safety between tPA and urokinase.<sup>105</sup> A randomized clinical trial comparing urokinase and recombinant tissue plasminogen activator (rtPA) noted a slight improvement in successful recanalization with rtPA in all infrainguinal segments treated ( $p < 0.05$ ).<sup>106</sup> A total of 120 patients at a single institution presenting with acute or subacute infrainguinal thrombotic occlusion were studied. At 6 months, the group treated with rtPA had improved claudication scores and a lower rate of limb amputation than the urokinase group, although these differences did not achieve statistical significance. Local hematomas were more common in the rtPA group, and there were no major bleeding complications in either group.

In a multicenter trial of thrombolysis or peripheral arterial surgery (TOPAS), the role of thrombolytic therapy vs surgical intervention in the setting of acute arterial occlusion of the lower extremity was evaluated.<sup>107</sup> This was a preliminary phase I trial designed to assess the dose ranging, safety, and efficacy of three doses of urokinase in comparison with surgery. In this randomized clinical trial, 213 patients who had lower extremity ischemia for up to 14 days were studied. No difference was observed in 1-year mortality or amputation-free survival between the urokinase-treated patients and those undergoing surgery. Open surgical procedures were avoided in 45.8% of patients randomly assigned to receive urokinase. The TOPAS investigators published their follow-up study, in which 548 patients were randomly assigned to either thrombolytic therapy or surgery to treat acute lower-extremity ischemia within 14 days of onset.<sup>108</sup> The primary end point of the study, amputation-free survival at 6 months, was similar for both groups (urokinase, 71.8%; surgery, 74.8%;  $p = 0.43$ ). There was a significant increase in the rate of major hemorrhage in the urokinase group compared with the surgery group, and four patients treated with urokinase sustained intracranial hemorrhage,

one of which was fatal. The only apparent benefit of urokinase was that fewer patients required open surgical procedures. At the end of 6 months, 31.5% of urokinase-treated patients had not required an open surgical procedure. In the absence of conventional evidence demonstrating benefit such as improved limb salvage, decreased mortality, or lower cost, thrombolysis for acute lower-extremity ischemia cannot be regarded as the standard of care for routine use in this clinical setting. It remains, however, a reasonable therapeutic option for selected patients in whom the risks of emergency surgical therapy are determined to outweigh the risks of thrombolysis.

Because of study heterogeneity, few conclusions can be drawn from the data except that thrombotic or embolic arterial occlusive lesions may be lysed by regional thrombolytic therapy, especially when given within 2 weeks. Chronic thromboatherosclerotic lesions are less responsive than thromboembolic occlusions and usually require adjunctive balloon angioplasty or surgery to prevent rethrombosis. In the latter circumstance, thrombolytic therapy preceding surgery might improve outcomes by clearly defining offending lesions and the distal arterial anatomy, as well as improving outflow and collateral circulation. Thrombolytic therapy appears most useful for distal thromboembolic occlusions in surgically inaccessible small arteries of the forearm, hand, leg, and foot, or in patients who are too ill to undergo surgery. In patients with acute renal or visceral arterial emboli identified at angiography, direct thrombolytic therapy may rarely achieve more rapid reperfusion than surgical thrombectomy.<sup>109–111</sup>

Recent developments concerning the availability of urokinase in the United States warrant additional attention as rtPA is now the only available thrombolytic agent that is commonly used for peripheral arterial thrombolysis. Additional lots of urokinase will not be released by the manufacturer until validation of testing for infectious agents has been completed. This resulted from significant good manufacturing practice deviations noted during a Food and Drug Administration inspection in the fall of 1998. The existing literature would appear to support the use of rtPA as a substitute for urokinase for peripheral arterial thrombolysis. In the STILE (Surgery versus Thrombolysis for Ischemia of the Lower Extremity) study, rtPA was as effective and as safe as urokinase.<sup>105</sup> In a randomized, open trial of 32 patients comparing rtPA and urokinase, rtPA resulted in faster initial lysis, although the 24-h and 30-day success was not significantly different.<sup>96</sup> An excellent review of thrombolysis for peripheral arterial occlusive disease was prepared by the Working Party on Thrombolysis, an international group of angiologists, hematologists, interventional radiologists, and vascular surgeons.<sup>112</sup> This review includes a summary of the literature on the use of peripheral thrombolysis as well as a table of reported dosage schemes for all available thrombolytic agents.

There have been reports of intraoperative intra-arterial thrombolytic therapy in patients undergoing thromboembolism.<sup>113–119</sup> Streptokinase, urokinase, and rtPA have all been used in varying doses instilled directly into the distal arterial tree after balloon-catheter embolectomy. Early reports are encouraging and demonstrate angio-

graphic evidence of improved clearance of distal thromboemboli not accessible to catheter thrombectomy with no apparent increase in bleeding complications. Some have found that additional thrombi could be mechanically removed after intra-arterial thrombolytic therapy.<sup>116</sup> Whether this approach will lead to improved limb salvage is unknown. The only randomized trial to date (and to our knowledge) comparing placebo and different dosages of intra-arterial urokinase infusion during lower limb revascularization in 134 patients documented the safety of this adjunct, but could detect no improvement in clinical outcomes.<sup>120</sup>

## PERIPHERAL VASCULAR RECONSTRUCTIVE SURGERY

### *Vein Grafts and Arterial Prostheses*

The superior patency of vein grafts is documented by a single, multicenter, randomized trial comparing saphenous vein grafts with expanded polytetrafluoroethylene (PTFE) prostheses for lower-extremity arterial reconstructions.<sup>121</sup> 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 ( $p < 0.001$ ). 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. More-recent series demonstrate improved patency rates with no major differences between reversed and nonreversed *in situ* vein grafts in which the valves are rendered incompetent.<sup>122,123</sup> 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 PTFE.<sup>124–126</sup> 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.<sup>127</sup> 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 (smooth muscle cell proliferative lesions). 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.<sup>127,128</sup> 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.

Despite some studies in experimental animals suggesting that antiplatelet therapy reduces neointimal hyperpla-

sia,<sup>129-131</sup> there are conflicting reports that show no effect.<sup>132,133</sup> Furthermore, it is doubtful that antiplatelet therapy prevents neointimal hyperplasia in humans.<sup>134,135</sup> The progressive narrowing of saphenous vein aortocoronary bypass grafts seen on follow-up angiograms is caused by neointimal hyperplasia<sup>136</sup> and is not mitigated by treatment with aspirin and dipyridamole.<sup>137</sup>

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 never 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 reepavement of the graft with endothelium. Arterial prostheses, however, are highly thrombogenic at the time of implantation and remain so.

Studies with <sup>111</sup>In-labeled platelets in humans demonstrate marked uptake of labeled platelets on femoropopliteal bypass prostheses of Dacron or PTFE, but little or no uptake on vein bypasses in the same position.<sup>138,139</sup> Treatment with aspirin plus dipyridamole significantly reduces labeled platelet uptake on femoropopliteal bypass prostheses but has no effect on vein bypasses because of the low baseline level of platelet accumulation.<sup>138</sup> In similar studies, aspirin plus dipyridamole decreased uptake of labeled platelets on aortofemoral bypass prostheses, but other antiplatelet agents had no effect.<sup>139-142</sup> Other studies in patients with Dacron aortofemoral bypass prostheses show continued uptake of labeled platelets on these prostheses when studied years after implantation.<sup>142,143</sup> This points out the difference in healing responses between man and experimental animals, which develop an endothelialized neointima that completely covers the luminal surface of large aortic and iliac prostheses within months to years after implantation.<sup>144-146</sup>

### *Reconstruction of High-Flow Arteries*

In vascular reconstructions involving high-flow, low-resistance arteries > 6 mm in diameter (aortoiliac, femoral, major visceral, renal, and proximal brachiocephalic vessels), thrombotic occlusion is unusual, and 5- to 10-year patency rates in the range of 80 to 90% can be expected.<sup>147</sup> Antithrombotic therapy is not indicated for such cases. An exception to this is axillofemoral bypasses that are long, are vulnerable to thrombotic occlusion, and have low patency rates.<sup>147</sup>

### *Reconstruction of Low-Flow Arteries*

Reconstruction of small arteries with flow rates of < 200 mL/min are prone to thrombosis, particularly if the bypass is long and crosses a flexion point at the knee or the groin. Such bypasses are more vulnerable to thrombotic occlusion than large-diameter, high-flow reconstructions, because an equivalent reduction in lumen from thrombus or anastomotic neointimal hyperplasia is much more likely

to critically impair blood flow. Effective antithrombotic therapy would theoretically enhance patency and extend the functional longevity of small-vessel reconstructions.

### *Antiplatelet Agents*

There are six randomized trials of antiplatelet therapy in patients with peripheral arterial bypasses.<sup>148-153</sup> In the two studies in patients undergoing prosthetic femoropopliteal bypass, aspirin plus dipyridamole therapy was started preoperatively<sup>148,149</sup>; both of these trials demonstrated a statistically significant reduction in prosthetic bypass occlusion. However, because these two studies had small numbers of patients in the treatment and control groups, the results are not definitive. In contrast, a larger study of 100 patients by Kohler et al<sup>150</sup> demonstrated no protective effect of aspirin plus dipyridamole.<sup>150</sup> However, this study differed in that antiplatelet therapy was started postoperatively. In addition, only one third of the patients had prosthetic bypasses, which are more vulnerable to thrombotic occlusion and would therefore be more likely to demonstrate a benefit of antiplatelet therapy. Based on the extensive experience in patients with saphenous vein aortocoronary bypass grafts,<sup>154-157</sup> the timing of antiplatelet therapy is probably important because early perioperative events, such as platelet accumulation at sites of vascular injury, are important in causing thrombotic occlusion; this indicates that antiplatelet therapy needs to be started early. A large study of 148 prosthetic grafts by Clyne et al<sup>151</sup> emphasizes this point and is helpful because it reconciles the differences between other trials in patients undergoing peripheral bypass. The treated patients in the study by Clyne et al<sup>151</sup> received preoperative and intraoperative IV dipyridamole. Postoperatively, they were treated with aspirin plus dipyridamole for 6 weeks. There was a significant and marked reduction in occlusion among treated patients who had prosthetic reconstruction; in treated patients with saphenous vein reconstructions, there was a nonsignificant trend suggesting benefit.<sup>151</sup> Taken together, these studies suggest that antithrombotic therapy started before (but not after) surgery may improve patency of lower-extremity bypasses, particularly when a vascular prosthesis is implanted.

A large multicenter trial of 549 patients from Great Britain focused on patients undergoing saphenous vein femoropopliteal bypass.<sup>152</sup> These investigators found no differences in patency rates between patients treated with aspirin and dipyridamole and control patients at an average follow-up of 24 months. However, they found that patients who received antiplatelet therapy had a significantly lower incidence of MI and stroke during follow-up; there was no significant difference in overall mortality between the two groups.<sup>152</sup> Another important finding from the British study, in which aspirin plus dipyridamole therapy was begun preoperatively, was that twice the number of wound hematomas and significantly greater transfusion requirements occurred in treated patients compared with control patients. The British trial is limited in that only saphenous vein femoropopliteal bypass recon-

structions were studied. In North America, most lower-extremity bypass reconstructions involve tibial arteries.<sup>158</sup> These longer and smaller reconstructions with lower flow rates are more vulnerable to thrombotic occlusion than are femoropopliteal bypasses, and the possibility remains that antithrombotic therapy would be beneficial in maintaining patency. The British trial was also plagued with problems in compliance (both among control and treated patients). In a subsequent retrospective subgroup analysis of patients in this trial, those with detectable serum salicylate as a marker of aspirin ingestion had significantly better patency than those with undetectable levels.<sup>159</sup>

The effect of ticlopidine on the patency of saphenous vein grafts performed for lower-extremity occlusive disease was assessed in a multicenter, placebo-controlled, randomized clinical trial of 243 patients.<sup>153</sup> Unlike the British study on aspirin and dipyridamole, patients undergoing both femoropopliteal and femorotibial bypass were included. At 24 months, the primary patency rate was 82% in the ticlopidine group and 63% in the placebo group ( $p = 0.002$ ). There were no differences in mortality or major ischemic events. Ticlopidine was well tolerated, and there was no difference in hematologic adverse events; however, the incidence of GI disorders (primarily diarrhea) was higher in the ticlopidine group.

The Antiplatelet Trialists' Collaboration performed an overview analysis of the effects of antiplatelet therapy on arterial or vascular graft patency from 11 randomized controlled trials containing > 2,000 patients.<sup>160</sup> Antiplatelet therapy, most often with aspirin, produced a highly significant ( $p < 0.0001$ ) reduction in occlusion during a mean follow-up period of 19 months.

Tangelder and others<sup>161</sup> recently reported a systematic review of randomized clinical trials of aspirin and anticoagulation in the prevention of graft occlusion and ischemic events after infrainguinal bypass. Trials were excluded from review if randomization was not concealed, if treatment regimens included agents other than aspirin or oral anticoagulants, or if central reconstructions or endarterectomies were included. Five studies on aspirin were analyzed.<sup>148,150,152,162,163</sup> In four of the studies, the bypass grafts were prosthetic, and in only one study were vein grafts used. The weighted relative risk for graft occlusion with antiplatelet therapy was 0.78 (95% confidence interval [CI], 0.64 to 0.95). The relative risk of graft occlusion supported antiplatelet therapy in all but one study.<sup>150</sup>

Dextran 40 has weak antiplatelet properties and has been used to prevent early lower-extremity bypass occlusion. This agent has been evaluated in a single randomized, multicenter trial in patients undergoing lower-extremity bypass.<sup>164</sup> The results showed significantly improved patency in patients treated with dextran 40 in the first week after operation. However, at 1 month there was no difference in patency between treated and control patients. These data suggest that the underlying problem predisposing to thrombosis remained after dextran 40 cleared the circulation. Patients who had prosthetic bypasses or long distal bypasses benefited most from dextran 40 treatment.

### Warfarin and Heparin

Oral anticoagulants have also been used to protect against thrombosis of arterial reconstructions. A randomized, prospective trial of 88 patients with reversed saphenous vein femoropopliteal bypasses demonstrated a significant reduction in bypass occlusion (18% among treated patients vs 37% among control patients;  $p < 0.03$ ) after a mean follow-up of 30 months.<sup>165</sup> There was a penalty, however, in that 12% of treated patients had to discontinue oral anticoagulant therapy because of major bleeding. This is of particular concern in elderly patients, who not only are more sensitive to warfarin<sup>166</sup> but frequently have large numbers of comorbid conditions and are vulnerable to intracranial hemorrhage.<sup>167</sup> Despite this, the same authors reported that patients in this study treated with warfarin had significantly improved survival rates compared with control patients.<sup>168</sup> Conflicting findings were reported in a larger study from Sweden, in which 116 patients undergoing vein and prosthetic lower-extremity bypasses were randomly assigned and followed for up to 3 years.<sup>169</sup> There were no statistically significant differences in patency, limb salvage, or survival rates between control and oral anticoagulant-treated groups. However, bleeding complications were more frequent in treated patients, who had a 5% incidence of serious or life-threatening bleeding problems. Another study of 130 patients demonstrated significant improvement in graft patency among patients treated with oral anticoagulants in comparison with those treated with antiplatelet therapy.<sup>170</sup> This study is remarkable for its long follow-up time, up to 10 years. An update of this study has been published, which extends these findings to 12 years.<sup>171</sup> Arterial graft patency and probability of survival were significantly improved in patients treated with oral anticoagulants.

Low-intensity oral anticoagulant therapy (international normalized ratio [INR], 1.5 to 2) combined with low-dose aspirin therapy (80 to 325 mg) is an attractive antithrombotic regimen that theoretically would retard thrombin generation in addition to inhibiting platelets.<sup>172</sup> Lower doses of these combined agents might offer superior antithrombotic effectiveness while minimizing hemorrhagic side effects. This combination was evaluated in a presented, but as-yet unpublished, multicenter study conducted in Department of Veterans Affairs hospitals.<sup>173</sup> Four hundred fifty-eight patients were randomly assigned to receive either aspirin alone (325 mg/d) or aspirin and warfarin (INR, 1.5 to 2.8). Treatment was initiated after surgery. Femoropopliteal bypass was performed in 37% of cases and femorotibial or femoropedal bypass in the others. The 4-year primary patency rates were not different (aspirin, 77% vs aspirin plus warfarin, 74%). Of note, approximately 75% of patients in the aspirin with warfarin group either had subtherapeutic warfarin levels or had discontinued warfarin therapy during the study.

The effect of the combination of warfarin and aspirin on the patency of infrainguinal vein bypass grafts at high risk for thrombosis was evaluated in a single-center, randomized clinical trial of 56 patients.<sup>174</sup> Aspirin dosage was 325 mg/d, and warfarin was given to maintain the INR be-

tween 2 and 3. Patients randomly assigned to the warfarin group received heparin anticoagulation postoperatively, which was converted to warfarin. Unlike the previously mentioned trials, only grafts at high risk for failure were included. These risk factors were marginal quality vein, poor arterial runoff, and previously failed bypass. Bypass to the tibial arteries was performed in 90% of patients. The 3-year primary patency rate (78% vs 41%) and the limb salvage rate were significantly higher in those randomly assigned to receive warfarin. Although there were more hematomas in the warfarin group (35% vs 3.7%), the overall complication rate was not different between groups. Although a benefit from the routine use of oral anticoagulation after uncomplicated femorotibial bypass procedures has not been demonstrated, patients considered to be at high risk for thrombosis might be a subgroup in which such a benefit exists, and they should be considered for postoperative anticoagulation.

The effect of oral anticoagulation compared with aspirin after infrainguinal bypass surgery was evaluated in a recently published multicenter randomized clinical trial of 2,690 patients.<sup>175</sup> Patients were randomly assigned to receive either oral anticoagulation (phenprocoumon or acenocoumarol; target INR, 3.0 to 4.5;  $n = 1,339$ ) or aspirin (80 mg daily;  $n = 1,351$ ). At a mean of 21 months' follow-up, there were 308 graft occlusions in the oral anticoagulation group compared with 322 graft occlusions with aspirin (hazard ratio, 0.95; 95% CI, 0.82 to 1.11), suggesting no overall benefit from either treatment. Subgroup analysis suggested that oral anticoagulants were beneficial in patients with vein grafts (hazard ratio, 0.69; 95% CI, 0.54 to 0.88), whereas aspirin had better results for nonvenous grafts (hazard ratio, 1.26; 95% CI, 1.03 to 1.55). The composite outcome of vascular death, MI, stroke, or amputation occurred 248 times in the oral anticoagulants group and 275 times in the aspirin group (hazard ratio, 0.89; 95% CI, 0.75 to 1.06). Patients treated with oral anticoagulants had more major bleeding episodes than those treated with aspirin (108 vs 56; hazard ratio, 1.96; 95% CI, 1.42 to 2.71). Although the overall results do not support routine use of oral anticoagulation after infrainguinal bypass, the results of the subgroup analysis suggest that additional study is needed to determine optimal antithrombotic therapy for different graft materials.

Heparin dramatically suppresses neointimal hyperplasia in experimental animals after balloon injury of arteries.<sup>176</sup> The smooth muscle cell antiproliferative effect, coupled with antithrombotic properties, provides a rationale to test long-term administration of low-molecular-weight heparin (LMWH) in patients undergoing lower-extremity bypass. In a study of 200 patients, LMWH administered for 3 months was compared with aspirin and dipyridamole in patients undergoing femoropopliteal bypass.<sup>177</sup> Not only was patency significantly better with LMWH treatment, but the effects persisted and became more dramatic with time. This suggested that early treatment with LMWH may have suppressed neointimal hyperplasia in its early stages of development. Although of great interest, confirmatory studies are required before this treatment can be recommended.

The use of LMWH compared with unfractionated heparin (UFH) for intraoperative anticoagulation during infrainguinal bypass surgery has been investigated in two randomized clinical trials.<sup>178,179</sup> In a multicenter trial of 201 patients, an LMWH, enoxaparin, was compared with UFH.<sup>178</sup> The agent to which the patient was randomly assigned was administered during surgery and for 10 days postoperatively. At the end of the 10 days, graft thrombosis occurred in 8% of patients randomly assigned to receive LMWH and in 22% of those treated with UFH ( $p = 0.009$ ). No difference in bleeding complications was observed. Conclusions regarding the use of LMWH on the basis of this study are limited owing to the brief follow-up period (10 days) and the inordinately high rate of graft thrombosis in the UFH group. Most series of infrainguinal bypass report short-term (within 30 days) thrombosis rates of 2 to 7%.<sup>180</sup> In the other study of LMWH for intraoperative anticoagulation, 18 patients undergoing infrainguinal bypass were randomly assigned to receive LMWH (dalteparin) or UFH.<sup>179</sup> Two early graft occlusions occurred in each group, and only one bleeding complication occurred in the UFH group. The small number of subjects limits meaningful clinical interpretation. A concern with the use of LMWH during vascular surgery is that it has a longer half-life than UFH and cannot be fully reversed with protamine. The lack of reversibility is probably not a major concern with infrainguinal bypass performed with vein graft, but it is of concern for procedures such as aortic revascularization and for bypass procedures performed with prosthetic materials such as PTFE that have a tendency for suture hole bleeding. Most surgeons do not routinely use therapeutic heparin or other anticoagulants beyond the intraoperative period.

On the basis of the experience cited above, antithrombotic therapy can be recommended for patients undergoing the following types of infrainguinal arterial bypass: (1) all bypasses in which prosthetic material is used; (2) long bypasses to small arteries (infrapopliteal); (3) complex reconstructions involving composite grafts or adjunctive endarterectomy; and (4) compromised operations (marginally adequate vein grafts, poor distal runoff, etc). For optimal protection, antithrombotic therapy should be started preoperatively and should consist of aspirin, 325 mg/d. Although it is not clear that preoperative dipyridamole is effective antithrombotic therapy, it has been used successfully in patients undergoing saphenous vein aorto-coronary bypass and does not appear to increase intraoperative bleeding. For patients at high risk for graft failure, the combination of warfarin (INR, 2 to 3) and aspirin (80 to 325 mg) can be recommended.

Long-term therapy is aimed at reducing the risk of stroke and MI in addition to possibly improving bypass patency.<sup>25,160</sup> For long-term antithrombotic therapy, aspirin, 81 to 325 mg/d, with or without dipyridamole, 75 mg three times daily, is recommended. It is not clear that dipyridamole is necessary, and further trials will be needed to settle this question. However, because of animal studies demonstrating that dipyridamole dramatically augments the antithrombotic effect of aspirin on artificial surfaces,<sup>181</sup> it may be prudent to use dipyridamole in conjunction with aspirin in patients with vascular

prostheses. For patients with complex, tenuous reconstructions, or for those who have thrombosed a primary reconstruction and thrombectomy has been successful in restoring secondary patency, warfarin therapy might be an appropriate choice in selected patients. Because of conflicting data and the risk of hemorrhage, warfarin, with or without aspirin, cannot be recommended for routine treatment in patients with lower-extremity bypasses.

### INTRAOPERATIVE ANTICOAGULATION

Intraoperative anticoagulation with heparin also deserves comment. Practices vary widely among vascular surgeons, and there is no consensus with regard to heparin dosage, method of administration (regional vs systemic), and timing.<sup>182</sup> The problem is compounded by the lack of controlled studies. Because of the experience with antiplatelet agents demonstrating that early antithrombotic therapy is important in determining postoperative patency, it is probable that intraoperative thrombus formation along suture lines, on prosthetic surfaces, and at areas of stasis proximal or distal to vascular clamps is detrimental. Therefore, maximal anticoagulation at the time of application of cross-clamps seems desirable. Also, the stimulus for thrombus formation and clotting is particularly intense with vessel trauma from manipulation, dissection, endarterectomy, and other forms of surgical injury that release large amounts of tissue thromboplastin and other clot-promoting substances as well as expose collagen and prosthetic surfaces to nonflowing, pooling blood. Amounts of heparin to achieve conventional systemic anticoagulation may not be adequate to prevent local clotting at the site of vascular reconstruction. This consideration, coupled with the highly variable response to heparin among patients undergoing vascular reconstruction,<sup>183–185</sup> argues for relatively high-dose heparin therapy. On the basis of these considerations, a rational heparin 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 heparin (50 to 80 min). Alternatively, some surgeons routinely obtain baseline activated clotting times in the operating room and adjust heparin dosage to maintain a twofold prolongation of the activated clotting time.

Most vascular surgeons routinely use systemic heparin anticoagulation during aortic revascularization while the aorta is clamped. Other vascular surgeons do not routinely anticoagulate during aortic surgery on the basis that larger diameter, high-flow arteries do not have a significant predisposition to thrombosis. This issue was evaluated in a multicenter, randomized clinical trial of 284 patients undergoing elective abdominal aortic aneurysm repair.<sup>186</sup> There was no difference in the incidence of blood loss, transfusion requirement, or arterial thrombosis in either group. However, those treated with heparin 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 heparin.

At the end of the procedure, complete heparin reversal

with protamine sulfate is recommended to minimize bleeding complications, particularly if perioperative antiplatelet therapy is used. Many surgeons do not reverse heparin<sup>181</sup> with protamine because of the transient adverse effects of protamine on hemodynamics (decrease in cardiac output and BP), hemostasis (protamine-induced thrombocytopenia), and, rarely, anaphylaxis. Life-threatening anaphylaxis occurs almost exclusively in diabetics who have received neutral protamine hagedorn (NPH) insulin in the past<sup>187</sup>; the frequency of this complication is 0.6 to 3.0%.<sup>188,189</sup> The need for heparin reversal with protamine was questioned in a single-center, randomized clinical trial of 120 patients undergoing peripheral vascular surgery.<sup>190</sup> In this double-blinded study, patients randomly assigned to receive protamine had no difference in blood loss, bleeding complications, or transfusion requirement compared with those administered saline solution. It should be noted that the heparin dosage used in this study was limited to a single dose of 90 U/kg. When using a higher dosage of heparin, as recommended above, failure to administer protamine would potentially result in significant bleeding complications, particularly with procedures that are associated with a higher risk of bleeding such as aortic reconstruction. Withholding treatment with protamine after procedures that are associated with a greater risk of thrombosis than bleeding, such as femorotibial bypass, would appear to be reasonable.

### Carotid Endarterectomy

In patients undergoing carotid endarterectomy, aspirin therapy may be an important adjunct. The goal of anti-thrombotic 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 <sup>111</sup>In-labeled platelets document marked deposition of platelets at the endarterectomy site immediately after operation.<sup>191,192</sup> The intensity of platelet accumulation decreases over time, possibly because of re-endothelialization of the endarterectomy site.<sup>191</sup> In one study of 22 patients, treatment of patients undergoing carotid endarterectomy with aspirin plus dipyridamole significantly decreased <sup>111</sup>In-labeled platelet deposition and appeared to decrease the incidence of perioperative stroke.<sup>192</sup> A study of 125 patients in which the benefit of aspirin therapy for longer periods after carotid endarterectomy was assessed has been reported.<sup>193</sup> Patients receiving aspirin, 650 mg twice daily started on the fifth postoperative day, had a slight but significant reduction in unfavorable end points when considered together (continuing transient ischemic attacks, 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 to 100 mg/d, with placebo after carotid endarterectomy.<sup>194</sup> Therapy was started 1 week to 3 months after operation, and no significant benefit of very-low-dose aspirin therapy was detectable. However, as with lower-extremity bypass operations, 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, 75 mg/d, vs placebo in 232 patients; therapy was started preoperatively and was associated with a marked reduction in intraoperative and postoperative stroke.<sup>195</sup> Data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) may shed additional light on the role of aspirin therapy and dosage after endarterectomy. Perioperative stroke occurring < 30 days after carotid endarterectomy was significantly lower among NASCET patients receiving relatively high-dose aspirin therapy (325 to 650 mg twice daily) in comparison with those receiving no aspirin or aspirin, 325 mg/d.<sup>196</sup> This striking finding was found on *post hoc* subgroup analysis and needs to be confirmed by a randomized study.

The recently reported results from the ASA (acetylsalicylic acid) and Carotid Endarterectomy (ACE) Trial Collaborators did not confirm the observations from NASCET that showed fewer perioperative strokes in patients given higher doses of aspirin.<sup>197</sup> The ACE trial was a multicenter, randomized, double-blind, clinical trial in which 2,849 patients scheduled for carotid endarterectomy were randomly assigned to receive one of four aspirin doses (81, 325, 650, and 1,300 mg). Aspirin therapy was started before surgery and continued for 3 months. The combined rate of stroke, MI, and death was lower in the low-dose groups (81 and 325 mg) than in the high-dose groups at 30 days (5.4% vs 7.0%;  $p = 0.07$ ) and at 3 months (6.2% vs 8.4%;  $p = 0.03$ ). Because many patients would be taking higher doses of aspirin before randomization into the study, and surgery would be performed before washout of the platelet effect from the previous dose, a separate efficacy analysis was performed of patients previously taking < 650 mg aspirin who were randomly assigned  $\geq 2$  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%;  $p = 0.002$ ; 4.2% vs 10.0%;  $p = 0.0002$ , respectively).

On the basis of these considerations, perioperative aspirin therapy, 81 to 325 mg daily, 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 incomplete reversal with protamine of intraoperative heparin, hypertension, and perioperative antiplatelet therapy.<sup>198,199</sup> If intraoperative heparin is not fully reversed or continuous heparin anticoagulation is administered postoperatively, perioperative aspirin therapy would potentially increase the incidence of hematomas and other bleeding complications.

It is unknown whether aspirin therapy will prevent or delay the onset of transient ischemic attacks and strokes in patients with asymptomatic cerebrovascular disease. Indirect evidence from the Department of Veterans Affairs asymptomatic carotid stenosis study suggests that aspirin may be beneficial in patients with advanced stenoses who

do not undergo carotid endarterectomy.<sup>200</sup> A surprising 16% of patients randomly assigned to medical therapy were intolerant and had to discontinue aspirin therapy.<sup>201</sup> The incidence of neurologic events was significantly higher among these patients than in those who continued aspirin therapy.<sup>200</sup>

The long-term protective effects of aspirin on stroke rate for asymptomatic patients with  $\geq 50\%$  carotid stenosis are unclear. In a double-blind, placebo-controlled trial in which 372 asymptomatic patients with  $\geq 50\%$  carotid stenosis were randomly assigned to receive 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.<sup>202</sup> 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.<sup>203,204</sup> Data from retrospective studies suggest that antiplatelet therapy does not reduce the incidence of recurrent carotid artery stenosis.<sup>205,206</sup> A randomized trial confirmed that treatment with aspirin and dipyridamole does not prevent symptomatic or asymptomatic recurrent stenosis after carotid endarterectomy.<sup>207</sup>

## RECOMMENDATIONS

*Preamble:* For patients with clinical evidence of cerebrovascular disease or coronary artery disease, the recommendation for aspirin use is grade 1A. The following recommendations refer to patients who do not have evidence of cerebrovascular disease or coronary artery disease.

### *Chronic Extremity Arterial Insufficiency*

1. Aspirin alone or in combination with dipyridamole may modify the natural history of intermittent claudication from arteriosclerosis. In addition, because these patients are at high risk of future cardiovascular events (stroke and MI), we recommend treatment with life-long aspirin therapy (81 to 325 mg/d) in the absence of contraindications (grade 1C+).
2. Clopidogrel may be superior to aspirin in reducing ischemic complications in patients with peripheral vascular disease and intermittent claudication, and we recommend that clinicians consider clopidogrel for treatment (grade 2A).
3. We recommend that pentoxifylline should *not* be routinely used in patients with intermittent claudication (grade 1B).
4. For patients experiencing disabling claudication, particularly when lifestyle modification alone is ineffective and revascularization cannot be offered or is

declined by the patient, we recommend a trial of cilostazol therapy (grade 2A). Cilostazol is not recommended for routine use in all patients with intermittent claudication because of its high cost and modest clinical benefit.

### *Acute Extremity Arterial Insufficiency*

1. We recommend that patients who suffer acute arterial thrombi or emboli undergo systemic anticoagulation with heparin to prevent proximal and distal thrombotic propagation. We recommend the use of heparin followed by oral anticoagulation to prevent recurrent embolism in patients undergoing thromboembolectomy (grade 1C).

2. We recommend that intra-arterial thrombolytic therapy be considered in patients with short-term (< 14 days) thrombotic or embolic occlusive disease provided that there is a low risk of myonecrosis developing during the time to achieve revascularization by this method (grade 2B).

### *Peripheral Vascular Reconstructive Surgery*

1. We recommend that clinicians do *not* use antithrombotic therapy to maintain patency of vascular reconstructions involving high-flow, low-resistance arteries > 6 mm in diameter in the absence of other indications for antithrombotic therapy (grade 1C). However, if aspirin therapy is indicated as a result of arteriosclerotic disease, we recommend life-long aspirin therapy in these patients to reduce long-term cardiovascular morbidity and mortality (grade 1C+).

2. We recommend that clinicians use aspirin (81 to 325 mg/d) in patients having *prosthetic*, femoropopliteal bypass operations, and antiplatelet therapy should be begun preoperatively (grade 1A). The addition of dipyridamole (75 mg three times daily) to aspirin may provide additional benefit (grade 2B).

3. In patients undergoing saphenous vein femoropopliteal or distal bypass, we recommend the use of aspirin therapy, 81 to 325 mg/d, to reduce the incidence of MI and stroke (grade 1C+). We recommend that clinicians administer life-long aspirin therapy in these patients (grade 1C+). In patients unable to take aspirin, we recommend that clinicians use clopidogrel (grade 1C+).

### *Anticoagulation*

1. We recommend that clinicians use long-term oral anticoagulation with warfarin with or without aspirin in selected patients after infrainguinal bypass and other vascular reconstructions (grade 2B). For patients undergoing infrainguinal bypass who are at high risk of graft thrombosis, we recommend combination treatment of warfarin and aspirin. (grade 1A).

2. We recommend that patients undergoing major vascular reconstructive operations undergo systemic

anticoagulation with heparin at the time of application of cross-clamps (grade 1A). The best route of administration (regional vs systemic) and optimal doses are unknown, and the desirability of reversing or not reversing heparin by protamine sulfate has not been established. Heparin reversal is subject to wide practice variations among surgeons.

### *Carotid Endarterectomy*

1. We recommend that clinicians give aspirin, 81 mg to 325 mg daily, preoperatively and continue treatment indefinitely in patients undergoing carotid endarterectomy to prevent subsequent transient ischemic attacks and stroke (grade 1A).

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