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What is the Optimum Perioperative Drug Therapy Following Lower-Extremity Vein Bypass Surgery?

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While endoluminal procedures are now commonly done for symptomatic peripheral arterial disease, vein bypass remains the gold standard for revascularization. Lower extremity vein bypass procedure success is dependent on patient factors, surgical judgment and technique, including use of medications. Cardioprotective medications have proven efficacy to decrease morbidity and mortality, but their use to improve graft patency is less well known. We review the up to date use of medications with known vascular effects that may promote graft success, as well as decrease cardiovascular events in this high risk patient group.
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Modifiable and Nonmodifiable Factors Related to Vein Graft Patency: The Current State

SEVERE PERIPHERAL ARTERIAL disease (PAD) significantly worsens a patient's quality of life due to pain and impaired mobility. Although often morbid procedures, infrainguinal arterial vein graft revascularization remains the gold standard for severe, long-segment occlusive PAD. Based on the current evidence, the optimal treatment for TransAtlantic Inter-Society Consensus (TASC) C and D lesions is an autologous vein bypass.[1] Recent epidemiologic data (1996-2006) from the Medicare population suggest a 42% reduction in peripheral arterial bypasses during the last 10 years, with a concurrent 300% increase in endoluminal procedures.[2] These data suggest that patients who present for peripheral bypass may be sicker, with long-segment occlusions, and possibly more difficult to revascularize segments. Thus, ways to optimize vein bypass success becomes paramount. Medical therapies, proven in cardiovascular disease, are an attractive set of tools to improve graft success by multiple different mechanisms (Fig 1).

Broadly, modifiable factors to improve infrainguinal bypass success include anatomical factors, such as ensuring adequate arterial inflow pressure, choosing the best outflow artery and vein conduit (Table 1). For example, a vein graft diameter >3.5 mm, use of saphenous vein versus nonsaphenous, and shorter rather than longer length grafts have a higher overall success rate.[3] Patient selection, medical therapies, postoperative surveillance and timely intervention are also important. For example, intensive graft surveillance confers a benefit in most studies,[4] with an improvement in assisted graft patency by ~20%.[5]

Analysis of graft outcomes suggests the primary factors of amputation-free survival are not necessarily changeable. Importantly, hemodialysis dependence, tissue loss, age older than 75 years, anemia, and coronary artery disease were primary factors for decreased amputation-free survival.[6] In this patient cohort of ~2,000 patients, medications such as antiplatelet agents, β-blocker, or cholesterol-reducing agents did not affect amputation-free survival, possibly because of common usage (>50%) or insufficient power to detect small therapeutic benefits.

Race and gender are also factors in determining vein graft success, and patency is worse for African-American women as compared to Caucasian men.[7] In this series, best medical therapy was also prescribed less commonly to African Americans. Recent data from ~15,000 patients who underwent infrainguinal lower-extremity bypass suggest lower age, African-American race, and diabetes are associated with increased early graft failure (eg, 30 days). These data highlight that intrinsic patient factors play a large role in graft success or failure.[8]

Recent series have characterized best medical practice and graft outcomes in patients autologous peripheral vein bypasses. The Project of *Ex-Vivo* Graft Engineering via Transfection III (PREVENT III) was a multicenter trial, which, although negative for the primary molecular therapy outcome, yielded a wealth of up-to-date practice data. Of note, primary patency of 61%, assisted primary patency of 77%, secondary patency of 80%, and limb salvage of 88% were

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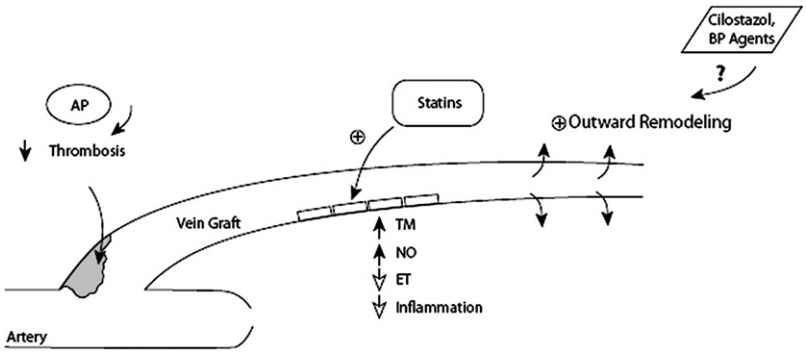

Figure 1 Proposed and known effects of medications on vein grafts. This figure highlights potential positive medication actions on a vein graft. Some of these mechanisms are well-accepted, such as the antiplatelet's (AP) antithrombotic effect. Many of the statin's actions have been derived from in vitro and small animal models. Whether cilostazol, a PDE_3 inhibitor or standard antihypertensives benefit vein grafts remodeling is reasonable speculation. BP, blood pressure; ET, endothelin; NO, nitric oxide; TM, thrombomodulin.

documented in patients with both saphenous as well as composite vein bypass.[9] Medical therapies were used variably in this patient cohort. Antithrombotic and β-blocker usage was 76% and 48%, respectively, and increased at discharge, suggesting acknowledgement of these important medical therapies. Lipid-lowering drugs were taken by less than half of the patients at baseline, including those with a stated history of hyperlipidemia.[10]

The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, a randomized controlled trial comparing endovascular with open surgery in patients with severe PAD, yielded important information. In this group of patients undergoing vein bypasses, overall amputation-free survival was approximately 60% at 5 years, underscoring the systemic severe nature of PAD.[11] In this cohort, only ~35% of patients were taking a statin, while 50% to 60% were on antithrombotic therapy, which suggests a large gap in ensuring best medical therapy.

From this selected review of the current state, two issues are present. First, ensuring patients with PAD are prescribed the appropriate cardioprotective medications is essential, supported by strong guidelines, and may confer a survival advantage.[12,13] Second, a key question is if, and by how much, can pharmacological agents, such as antithrombotics, cholesterol-reducing agents, and antihypertensives, improve graft patency (Table 2). Little direct evidence exists, in part due to the heterogeneous nature of the patients, disease severity, and procedures performed. Whether these agents can prevent or delay the neointimal hyperplasia that often affects the graft, and "give time" to allow interventional correction will require further study.

Table 1 Factors for Arterial Vein Bypass Success

Modifiable	Nonmodifiable
Adequate arterial inflow	Age
Patient selection	End-stage renal failure
Smoking cessation	Conduit quality
Pharmacologic regimen	Coronary heart disease
Graft surveillance	

Antiplatelet Anticoagulant Therapy

Antiplatelet therapy is standard for all patients with PAD and thus as an indication solely to improve vein bypass patency is a nonissue. Whether the type of antiplatelet therapy is more or less beneficial for autologous grafts remains open to question, particularly with new agents on the horizon. Current agents include aspirin (ASA), clopedigrel (Plavix, Sanofi Aventis, Bridgewater, NJ), dipyridamole-ASA (Aggrenox), heparin agents, vitamin K antagonist (VKA), and intravenous dextran.

Updated guidelines for antithrombotic therapy for PAD have been published, and ASA is the primary therapy.[14] ASA works by irreversibly inhibiting cyclooxgenase and is a highly effective medication for secondary cardiovascular morbidity and mortality prevention.[15] For autologous vein infrainguinal bypasses, ASA at 75 to 100 mg daily is recommended, and should be begun preoperatively.[15] Similarly, a recent Cochrane Database review suggest that long-term use of antiplatelet therapy started prior to surgery results in improved graft patency.[16]

Perioperative adjunctive anticoagulation, such as low molecular weight heparin, intravenous heparin, and dextran all do not have sufficient evidence for their routine use in autologous vein bypasses.[14] The exception to this may be the use of low molecular weight heparin in patients who have a compromised graft for limb salvage.[17] Perioperative dextran (which I have used routinely for 36 hours post-graft) does not have evidence to support its routine use.[18]

Use of VKA therapy as compared with ASA alone has not shown a patency benefit, as suggested by a large Veteran's Affairs cooperative trial.[19] Indeed, vein bypass patency was not improved, but deaths were significantly greater with warfarin. The Dutch BOA study was a large randomized controlled trial of nearly 2,700 patients (undergoing mixed type

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