Aortocoronary Saphenous Vein Graft Disease
Pathogenesis, Predisposition, and Prevention

Joseph G. Motwani, MD; Eric J. Topol, MD

Abstract—Aortocoronary saphenous vein graft disease, with its increasing clinical sequelae, presents an important and unresolved dilemma in cardiological practice. During the 1st month after bypass surgery, vein graft attrition results from thrombotic occlusion, while later the dominant process is atherosclerotic obstruction occurring on a foundation of neointimal hyperplasia. Although the risk factors predisposing to vein graft atherosclerosis are broadly similar to those recognized for native coronary disease, the pathogenic effects of these risk factors are amplified by inherent deficiencies of the vein as a conduit when transposed into the coronary arterial circulation. A multifaceted strategy aimed at prevention of vein graft disease is emerging, elements of which include: continued improvements in surgical technique; more effective antiplatelet drugs; increasingly intensive risk factor modification, in particular early and aggressive lipid-lowering drug therapy; and a number of evolving therapies, such as gene transfer and nitric oxide donor administration, which target vein graft disease at an early and fundamental level. At present, a key measure is to circumvent the problem of vein graft disease by preferential selection of arterial conduits, in particular the internal mammary arteries, for coronary bypass surgery whenever possible. (Circulation. 1998;97:916-931.)

Key Words: atherosclerosis ■ bypass ■ grafting ■ risk factors ■ prevention

The first aortocoronary saphenous vein graft implantation in a human being by Garrett and colleagues in May 1967 and the subsequent pioneering work of Favaloro ushered in the era of surgical revascularization for the global epidemic of ischemic heart disease. This major advance in surgical practice afforded an effective treatment for intractable angina and also a means of markedly improving long-term prognosis in certain patient subgroups. Ironically, with demonstration of the dramatically benefits obtainable by saphenous vein grafting came recognition of the ultimately palliative nature of the operation, due to the accelerated atherosclerosis that develops within the grafted saphenous vein conduits. During the first year after bypass surgery up to 15% of venous grafts occlude, between 1 and 6 years the graft attrition rate is 1% to 2% per year, and between 6 and 10 years it is 4% per year. By 10 years after surgery only 60% of vein grafts are patent (Fig 1) and only 50% of patent vein grafts are free of significant stenosis. In addition, native coronary artery disease progresses in ~5% of patients annually. Reflecting this graft and native vessel attrition, angina recurs in up to 20% of patients during the first year after saphenous vein grafting and in ~4% of patients annually during the ensuing 5 years. Further revascularization, either reoperative bypass surgery or percutaneous intervention, is required in ~4% of patients by 5 years, 19% of patients by 10 years, and 31% of patients by 12 years after initial bypass surgery (Fig 2). Both surgical and percutaneous forms of repeat revascularization have considerable limitations. As compared with initial surgery, reoperation carries a higher mortality rate (3% to 7%) with a high rate of perioperative myocardial infarction (4% to 11.5%). Coronary atheroembolism from diseased vein grafts is a major cause of the morbidity and mortality associated with reoperation. Redo surgery is also associated with less complete relief of angina and with reduction in saphenous vein graft patency as compared with initial bypass surgery. As increasing numbers of patients undergo second and third reoperations, the perioperative morbidity and mortality escalates further and the clinical benefits diminish. Percutaneous treatments for vein graft disease continue to be hindered, despite recent adjunctive therapies, by a high periprocedural morbidity resulting from distal embolization of atherothrombotic debris. Furthermore, subsequent event-free survival is low, due to both frequent restenosis at the treated lesion site, even after stent placement, and also to a high rate of late clinical events from untreated lesions that appear angiographically “nonsignificant” at the time of initial intervention.

I. Pathogenesis of Saphenous Vein Graft Disease

“Saphenous vein graft disease” is composed of three discrete processes: thrombosis, intimal hyperplasia, and atherosclerosis. These processes, although more or less temporally distinct, are interlinked pathophysiologically in the evolution of vein graft disease.
Thrombosis
Between 3% and 12% of saphenous vein grafts occlude, with or without symptoms, within the first month after bypass surgery.6,7 At this early stage, the principal underlying mechanism is graft thrombosis (Fig 3),18 caused by a combination of alterations in the vessel wall, changes in blood rheology, and altered flow dynamics, as classically defined in Virchow’s triad.

Even when performed under optimal conditions, the harvesting of venous conduits is associated with focal endothelial disruption.19 In particular, the high pressure distension used to overcome venospasm during harvesting causes prominent endothelial cell loss and medial damage.19 Loss of the endothelial monolayer results in the accumulation of fibrin on the luminal surface, the adherence of platelets and neutrophils,20,21 and a reduction in tissue plasminogen activator (tPA) production.22 Endothelial loss also activates the extrinsic coagulation cascade by tissue factor that is constitutively expressed in the exposed subendothelium.20 Tissue factor is also expressed, within 2 hours of initiating cardiopulmonary bypass, on the surfaces of endothelial cells activated by inflammatory cytokines.20

Thrombomodulin is an important membrane-bound antithrombotic regulatory protein that forms a 1:1 complex with thrombin, leading to activation of the circulating anticoagulant molecule, protein C. The process of vein harvesting attenuates the activity of thrombomodulin by up to 30%, a further procoagulant effect.23

Additionally, the inherent antithrombotic properties of veins are comparatively weak. Heparan sulfate, a proteoglycan molecule with anticoagulant properties mediated by potentiation of antithrombin III (ATIII), is less prominent in the media and in the poorly developed internal elastic lamina of veins as compared with arteries.18 Production of nitric oxide (NO) and prostacyclin, both potent inhibitors of platelet activation, is lower in veins than in arteries, and NO production is further reduced by bypass grafting.24 The low fluid shear stress in grafted venous conduits, as compared with arteries, reduces the shear-dependent release of tPA, NO, and prostacyclin.25

Bypass surgery not only disturbs the local production of factors influencing hemostasis but also alters their circulating levels, with a particularly marked perioperative elevation of plasma fibrinogen, and these changes also favor a prothrombotic response.26,27

The propensity for early graft occlusion resulting from these prothrombotic effects may, on occasion, be amplified by technical factors that reduce graft flow, including intact venous valves, anastomotic stricture, or graft implantation proximal to an atheromatous segment. In addition, saphenous veins, particularly when denuded, are highly sensitive to circulating vasoconstrictors, including the most potent endogenous vasoconstrictor, endothelin-1.20 The circulating concentration of endothelin-1 shows a marked initial rise, followed by an additional slower increment, after the onset of cardiopulmonary bypass,26 and the resulting vasoconstrictor response may further attenuate flow and promote stasis. Additionally, in saphenous veins, the predominant vasomotor response to thrombin is a constrictor one, in contrast to the thrombin-mediated vasorelaxation that occurs, via endothelial receptors, in internal mammary arteries.29
Intimal Hyperplasia

Intimal hyperplasia, defined as the accumulation of smooth muscle cells and extracellular matrix in the intimal compartment, is the major disease process in venous grafts between 1 month and 1 year after implantation. Many veins exhibit mild intimal or medial fibrosis before grafting. Nonetheless, nearly all veins implanted into the arterial circulation develop further intimal thickening within 4 to 6 weeks, which may reduce the lumen by up to 25% (Fig 4A). This process, in itself, rarely produces significant stenosis. Nonetheless, intimal hyperplasia represents the foundation for later development of graft atheroma. In support of this proposal, the localized areas of “adaptive” intimal hyperplasia that occur in native human arteries have been defined by the American Heart Association Council on Arteriosclerosis as “atherosclerosis-prone regions.” The extensive intimal hyperplasia throughout the length of a vein graft may effectively create a diffuse atherosclerosis-prone region.

Neointimal hyperplasia, whether in the balloon-injured artery or in the grafted vein, follows a similar pathogenic sequence. Initially, medial smooth muscle cells proliferate in response to a number of growth factors and cytokines released from platelets and from activated endothelial cells and macrophages. This is followed by migration of smooth muscle cells into the intima, with subsequent further proliferation. Later, synthesis and deposition of extracellular matrix by activated smooth muscle cells leads to a progressive increase in intimal fibrosis and a reduction in cellularity. The endothelial cell plays a key role in regulating intimal growth through a number of tonic growth-inhibitory mechanisms. Endothelial loss markedly attenuates these growth-modulating effects. Furthermore, as neoendothelial forms, it does so over a layer of platelets and fibrin that has been deposited on the thrombogenic basement membrane. This nonocclusive thrombus is progressively organized into fibrotic tissue as the abundant platelet component releases growth factors, which promote ingress and proliferation of smooth muscle cells.

However, in contrast to the arterial injury model, in the venous graft the major component of intimal hyperplasia occurs after endothelial regeneration. Thus additional mechanisms operate in the grafted vein. One such mechanism relates to the transient ischemia that veins necessarily incur on implantation, with reperfusion after grafting. This “ischemia-reperfusion” cycle not only reduces endothelial production of antiproliferative mediators such as prostacyclin, NO, and adenosine but also induces marked superoxide radical formation that directly promotes smooth muscle cell proliferation. Loss of the vasa vasorum blood supply, on which veins are relatively more dependent than arteries, may also promote a continuing cycle of ischemia and fibrosis. Recent in vitro evidence also indicates that thrombin causes much more pronounced proliferation of smooth muscle cells in saphenous veins, as compared with internal mammary arteries.

Very recent evidence from a porcine model of saphenous vein grafting indicates that an additional mechanism for graft neointima formation may involve perivascular fibroblasts, which translocate through the media of newly placed vein grafts and differentiate into myofibroblasts, acquiring α-smooth muscle actin. The intima of human saphenous vein grafts retrieved during repeat bypass surgery exhibits a profile of cytoskeletal proteins similar to that of myofibroblasts in porcine vein grafts, suggesting a role for these cells in graft intimal hyperplasia in the clinical setting.

The acute, pronounced increase in wall stress incurred by saphenous veins on exposure to arterial pressures is another factor promoting intimal fibrosis. This increased wall stress, in the canine model, significantly upregulates vein graft intimal receptors for basic fibroblast growth factor (bFGF), a potent vascular smooth muscle cell mitogen released from damaged endothelial and smooth muscle cells. Furthermore, distension of veins under arterial pressure increases vein diameter and reduces mean blood velocity, both favoring decrease in shear stress, as comprehensively reviewed by Allaire and Clowes. The reduction in shear stress increases the shear-regulated production of a number of potent mitogens, including platelet-derived growth factor (PDGF), bFGF, and endothelin 1, and attenuates the production of growth inhibitors such as transforming growth factor-β and NO, thus shifting the balance toward smooth muscle cell proliferation and intimal hyperplasia.

Atherosclerosis

Beyond the first year after bypass surgery, atherosclerosis is the dominant process underlying the attrition of saphenous vein grafts and the eventual recurrence of ischemic symptoms. Although the progression of native vessel coronary disease is also important in symptom recurrence, angiographic studies indicate that among patients who present with unstable angina, non–Q-wave myocardial infarction, or Q-wave myocardial infarction after previous bypass surgery, the culprit lesion in 70% to 85% of cases is an atherosclerotic vein graft stenosis, often with superimposed thrombus.

Necropsy studies have found evidence of atheromatous plaques as early as 1 year after bypass surgery, but hemodynamically important stenoses resulting in recurrent symptoms rarely occur before 3 years after grafting, and the clinical impact of vein graft atheroma increases markedly after 5 to 7 years. The histological types and stages of atherosclerotic lesion development in native coronary arteries have been comprehensively reviewed by the AHA Council on Arteriosclerosis. Although the fundamental process of atheroma development and the predisposing factors (reviewed in detail in section II) are similar in vein grafts, certain temporal, histological, and topographic differences from native vessel disease exist.

Central among these differences is the rapidly progressive nature of the atherosclerotic process in saphenous vein grafts. As in other situations in which accelerated forms of atherosclerosis occur (for example, in chronic transplant rejection), a pivotal factor in the rapidity of progression of vein graft atheroma is chronic endothelial cell injury and dysfunction. Histologically, vein graft atheroma has more foam cells and inflammatory cells, including multinucleate giant cells, than native coronary atheroma with appearances similar to experimental models of immune-mediated atherosclerosis. This observation has even led certain investigators to propose an immunological basis for vein graft atheroma.
Morphologically, vein graft atherosclerosis tends to be diffuse, concentric, and friable with a poorly developed or absent fibrous cap and little evidence of calcification (Fig 4B), whereas native vessel atheroma is proximal, focal, eccentric, and nonfriable with a well-developed fibrous cap and frequent calcification (Fig 4C). Recent in vivo intravascular ultrasound evidence suggests that the focal compensatory enlargement observed in atherosclerotic native coronary arteries (“Glagov’s law”) does not occur in stenotic saphenous vein grafts.

The lipid handling of saphenous veins is also relatively proatherogenic, with slower lipolysis, more active lipid synthesis, and higher lipid uptake than in native coronary arteries.

Late Thrombotic Occlusion: Late graft thrombosis, resulting in recurrent myocardial ischemia, is a frequent occurrence in old, degenerated vein grafts with advanced atherosclerotic plaque formation. In one morphological evaluation, late thrombosis was observed in 69% of 173 resected, aged grafts among 103 (72%) of 143 patients undergoing repeat bypass grafting for recurrent, intractable symptoms. Thrombosis was particularly evident in grafts showing aneurysmal dilatation; all 16 grafts with this pathological change exhibited late thrombotic occlusion. Recently, Kockx et al observed a close spatial relationship between foam cell accumulation, pronounced smooth muscle cell loss, and cell death in segments of occluded vein grafts resected during repeat grafting. These investigators have proposed the existence of a foam cell-derived factor inducing intimal smooth muscle cell death with the resulting depletion of smooth muscle cells promoting plaque rupture and thrombosis.

II. Predisposing Factors for Saphenous Vein Graft Disease

Morphological Factors
A number of morphological factors have been associated with reduced vein graft patency.

Native Vessel Diameter
Roth and coworkers observed that 1-year vein graft patency was 90% if grafted vessel diameter was >1.5 mm at operation but only 65% if the diameter was \( \leq 1.5 \) mm (\( P < 0.01 \)). Cataldo et al observed a similar influence on graft patency of vessel diameter determined angiographically.

Grafted Vessel
Cataldo et al observed that the patency rate of vein grafts to the left anterior descending coronary artery was significantly higher than patency rate of vein grafts to right coronary or circumflex arteries. In contrast, Cosgrove et al observed no significant difference in patency rates of grafts to the three epicardial vessels.

Severity of Bypassed Proximal Stenosis
Roth and colleagues found that angiographic patency 1 year after bypass surgery was 90% for vein grafts (n = 105) anastomosed to arteries with proximal stenosis >70%, but only 80% for vein grafts (n = 113) placed to arteries with proximal stenosis <70% (\( P < 0.05 \)). It has been postulated that the greater competitive flow through a less severely stenosed native vessel predisposes to vein graft occlusion. However, Cosgrove and coworkers observed that angiographic patency 16 months after bypass surgery was 76.8% among 67 vein grafts to arteries with proximal stenosis <50% and 78.2% among 99 vein grafts to arteries with >50% stenosis (\( P = \text{NS} \)). Accordingly, the importance of competitive flow as a predisposing factor in vein graft occlusion remains contentious.

Age of Graft
Another area of controversy is whether normal or minimally diseased vein grafts should or should not be replaced during late reoperation. Campos et al evaluated 62 patients angiographically and found that of vein grafts that were normal or minimally diseased 6 years after bypass surgery, 79% remained patent and 71% were free of significant stenosis at 11 years. Similarly, Mehta et al observed a favorable long-term outcome of aged but angiographically normal vein grafts. However, other observational studies performed in the setting of redo surgery or percutaneous intervention have reported high incidences of late clinical events from aged venous conduits with angiographically “mild” disease.

Cigarette Smoking
Multivariate risk factor analyses based on morphological and angiographic studies have consistently implicated cigarette smoking as an important risk factor for the development of vein graft atheroma. Smoking is also a risk factor for both early and late graft thrombosis. The unexpected initial evidence from the European Coronary Surgery Study—that no apparent difference existed in clinical benefit or survival between smokers and nonsmokers after bypass surgery—has been challenged by the more recent long-term results of the Coronary Artery Surgery Study (CASS). Survival at 10 years after surgery was 77% among the 312 smokers compared with 82% among 468 nonsmokers (\( P = 0.025 \)) despite the smokers being a younger group (mean age, 49 years versus 53 years).

Follow-up of CASS registry patients revealed that cigarette smoking is an important predictor of recurrent angina during the first year after bypass surgery (relative risk, smoker:nonsmoker = 1.21; \( P = 0.009 \)). Evidence from CASS and from another recently published long-term evaluation emphasizes the much improved clinical outcome among patients who have stopped smoking after bypass grafting as compared with persistent smokers (reviewed under “Cessation of Smoking”).

Hyperlipidemia
The evidence implicating hyperlipidemia as a key risk factor in the development of vein graft atherosclerosis is as consistent and strong as it is for native coronary atheroma. Daida et al reviewed angiographic data from 284 patients and found that rates of obstructive atherosclerotic vein graft disease (\( \geq 70\% \) stenosis) 17 years after surgery were highly related to preoperative serum cholesterol levels (for serum cholesterol \( \leq 200 \) mg/dL, 12% of grafts were obstructed; for serum cholesterol \( \geq 240 \) mg/dL, 43% were obstructed; \( P < 0.005 \)). Campeau et al found that the development of new angiographic lesions 10 years after bypass surgery was predicted by higher levels of plasma cholesterol, VLDL, and LDL, and by...
lower HDL levels. Multivariate analysis of lipoprotein fractions indicated that lower levels of HDL cholesterol and higher levels of LDL apoprotein B best predicted new lesion development. Importantly, and in contrast to native coronary disease for which the evidence is weak, several studies have also emphasized the importance of hypertriglyceridemia as a risk factor in vein graft atherogenesis.

Solymoss and coworkers observed that late vein graft thrombosis is predicted by elevated ratios of total:HDL and LDL:HDL cholesterol. This prothrombotic influence relates not only to the well-defined effects of hyperlipidemia in promoting the formation of a lipid-rich plaque prone to rupture but also to increasingly recognized procoagulant effects. Oxidized LDL is especially potent in this respect, both stimulating the synthesis of plasminogen activator inhibitor I (PAI-1) and inhibiting the synthesis of tPA.

In accordance with these demonstrable effects of serum lipid disturbances in promoting vein graft disease, patients with hyperlipidemia exhibit a high incidence of late adverse clinical outcomes after bypass surgery, including myocardial infarction and need for further revascularization. Furthermore, as in native coronary disease, the combination of elevated serum triglycerides and low HDL is an important predictor of increased cardiac morbidity and increased cardiac and total mortality after bypass grafting.

In contrast to its importance as a predictor of reduced late graft patency, dyslipidemia does not appear to influence vein graft patency at 1 year after bypass surgery. This lack of influence is in keeping with the understanding that graft attrition during the first postoperative year results principally from early thrombotic occlusion related to rheological and technical factors rather than from vein graft atherosclerosis.

**Hypertension**

Systemic hypertension, a major risk factor for development of native coronary disease, has been found in the CASS registry cohort to predict increased overall morbidity, including stroke, in the first year after bypass surgery. However, a history of hypertension has not been found in the CASS registry to predict recurrent angina in either the first or subsequent postoperative years. Furthermore, angiographic and morphological studies have not found an association between hypertension and either early (first year) graft occlusion or late (6 to 12 years) atherosclerotic graft failure.

In contrast to this lack of demonstrable effect on the development of graft atheroma, several studies have implicated systemic hypertension as a risk factor for graft intimal hyperplasia. Of potential relevance in this regard is the finding that saphenous veins express abundant receptors for bFGF, an important smooth muscle mitogen, and high pressure distension is a potent stimulus for upregulation of these receptors. Indeed, the wall thickness of even ungrafted saphenous veins is significantly increased in hypertensive patients as compared with normotensive controls. Thus hypertension may have indirect rather than direct effects in vein graft atherosclerosis by promoting development of the “atherosclerosis-prone” foundation of intimal hyperplasia.

**Diabetes Mellitus**

Diabetes is an important risk factor for increased late mortality after bypass surgery. In one study, 5-year survival was 94% among 4522 nondiabetics but only 80% among 1132 diabetics; \( P < .0001 \). In another evaluation, a preoperative blood glucose level of \( \geq 140 \) mg/dL was predictive of increased late mortality after coronary bypass grafting among diabetic patients \( (P < .05) \). In the CASS registry, diabetes was an important predictor of recurrent angina in the second (but not the first) postoperative year and also a predictor of angiographic native vessel disease progression at 5 years after surgery. Furthermore, the saphenous vein of diabetic patients is functionally deficient as a conduit, demonstrating impaired production of the potent vasodilator, prostacyclin.

Despite these collective observations, the evidence from angiographic and pathological studies that diabetes promotes vein graft atherosclerosis is inconsistent: Some investigators have implicated diabetes as a risk factor for development of graft atheroma and others have not. However, all of these studies are retrospective; currently, there are no published prospective data on the influence of diabetes or its treatment on angiographic disease progression in vein grafts.

**Effect of Gender**

Female sex is associated with increased perioperative morbidity and mortality with coronary bypass surgery. The CASS registry data also show that women experience a higher rate of recurrent angina than men, both in the first and in subsequent postoperative years. In accordance with this higher symptom recurrence, Loop et al observed that 2-year vein graft patency was significantly lower in women (76.4%) than in men (82.1%) \( (P < .001) \). The reduced early graft patency in women is thought to be largely attributable to coronary vessel diameter. Women have smaller coronary arteries than men even after controlling for a number of indices of body size, including height, weight, body surface area, and body mass index. Despite increased vein graft attrition and the higher frequency of recurrent angina among women, survival rates at 5 years, 10 years, and 15 years after bypass grafting have been found to be equivalent in men and women. Furthermore, the women in these studies have been older than the men by a mean of 2 to 3 years.

There are currently no published data concerning the effect of estrogens on vein graft patency. However, a recently published evaluation found that 10-year survival after coronary bypass surgery among 92 women who received postmenopausal estrogen replacement therapy was significantly greater than among 1006 women who did not (81.4% versus 65.1%; relative risk, .38; \( P = .001 \)).

**Recently Identified Risk Factors**

Of the expanding profile of “new” risk factors implicated in coronary atherosclerosis, three have emerged as particularly relevant. These three factors—lipoprotein (a), homocysteine, and fibrinogen—have each been studied, to a varying degree, in the context of vein graft disease.

**Lipoprotein (a)**

Lipoprotein (a) \( [Lp(a)] \), a macromolecular complex composed of an LDL-like particle attached to a large, highly glycosylated
protein [apolipoprotein (a) or apo (a)], is an independent risk factor for premature coronary atherosclerosis. Underlying this risk is the accumulation of apo(a) in the atherosclerotic plaque and the potential for inhibition of fibrinolysis by Lp(a).

After coronary bypass surgery there is an acute, profound decrease of 40% to 60% in plasma Lp(a) on postoperative day 3, followed by a small but significant overshoot on day 10, possibly as part of the acute phase response, with restoration of preoperative levels at 4 to 6 weeks. Accordingly, postoperative plasma Lp(a) levels can be reliably determined 1 month after surgery at the earliest.

Although Lp(a) is almost absent from the normal saphenous vein, it shows a striking propensity for accumulation, together with apo B, in the intima of vein grafts, as well as in the coronary arterial wall of patients with prior bypass surgery. In 167 symptomatic patients undergoing cardiac catheterization who had undergone coronary bypass surgery 0.7 to 14.3 years earlier, Hoff et al observed that with stepwise increments in mean serum Lp(a), the prevalence of vein graft stenosis increased: 92% of patients with serum Lp(a) levels of 31.6 mg/dL or above had atheromatous vein graft narrowing. Other investigators have similarly observed that significant late vein graft narrowing or occlusion is related to elevated preoperative serum Lp(a) levels. In contrast, and as expected, the frequency of 1-year graft occlusion was found not to be associated with preoperative serum Lp(a) levels.

**Homocysteine**

A number of prospective and case-control studies have shown that even modest elevation of plasma homocysteine, as a result of nutritional and genetic factors, is an independent risk factor for coronary artery disease. Homocysteine appears to exert its prothrombotic and atherogenic effects through a number of mechanisms involving endothelium, platelets, and the coagulation cascade. Oral folate therapy reduces plasma homocysteine concentration, making identification of hyperhomocysteinemia in patients with coronary artery disease more than an academic exercise.

Only one study has assessed the effect of elevated plasma homocysteine on coronary bypass graft patency. This study focused on 1-year patency only and therefore could not evaluate the role of homocysteine in promoting vein graft atherosclerosis. In this cohort of 565 patients, no relationship was observed between preoperative serum homocysteine levels and the presence of occluded vein grafts or internal mammary grafts as determined angiographically at 1 year. However, of note, many factors including drug therapy, concomitant disease, and ethnic background, can substantially influence the result of a single plasma homocysteine estimation as was used in this study.

**Fibrinogen (and Other Hemostatic Factors)**

Prospective clinical studies have found a strong and independent association between plasma fibrinogen levels and the subsequent development of coronary artery disease, and cross-sectional angiographic studies have observed correlations between plasma fibrinogen and the extent of coronary artery disease. High levels of circulating fibrinogen predispose to ischemic heart disease by increasing plasma viscosity and platelet aggregability and by contributing to the initiation and development of the atherosclerotic plaque.

Marked activation of both coagulation and fibrinolytic systems, albeit with wide interindividual variation, occurs intraoperatively in patients undergoing cardiopulmonary bypass. The resulting alterations in hemostatic parameters may persist for up to 30 days after surgery. Compared with the preoperative level, plasma fibrinogen doubles by day 3 after surgery and is still markedly elevated on day 8 (both \( P < .0001 \)). Significantly higher day 3 and day 8 postoperative elevations of plasma fibrinogen and of thrombin-antithrombin complexes are observed among patients with one or more vein graft occlusion at 3 months (\( P < .05 \)). Patients with vein graft occlusion also showed lower basal preoperative tPA activity and Factor VIII levels (both \( P < .05 \)).

Clearly, larger and longer-term studies are required to determine any effect of plasma fibrinogen on the development of vein graft atheroma. However, the results of this small study suggest that markedly elevated perioperative plasma fibrinogen, and alterations in other hemostatic factors, may contribute to early thrombotic attrition of vein grafts.

Table 1 summarizes the predisposing factors for saphenous
III. Strategies for Preventing Vein Graft Disease

A. Established Strategies

Cessation of Smoking

In the CASS study, for patients who smoked at study entry and were randomized to bypass surgery, survival at 10 years was 68% among persistent smokers and 84% among those who stopped smoking within 6 months of surgery (relative risk of death, nonquitter:quitter = 1.73; P = .018). In contrast, among those randomized to medical therapy in CASS, the small difference in survival between persistent smokers and those who had stopped (71% versus 75%) was not statistically significant. The greater benefit of smoking cessation in the surgically treated patients alludes to the specific impact of smoking in reducing survival in this group through its effects in promoting vein graft disease rather than native vessel disease progression.

The CASS data have been complemented by a recently published 15-year prospective follow-up study of 415 patients after vein grafting. Compared with patients who stopped smoking since surgery, persistent smokers at 1 year after surgery had 2.3 times the risk of myocardial infarction (P = .04) and 2.5 times greater need for reoperation (P = .03). Even greater elevations of risk for myocardial infarction, reoperation, and angina pectoris were observed in patients still smoking 5 years after surgery. No statistically significant differences in outcome at 1 or 5 years were observed in this study between patients who had stopped smoking after surgery and nonsmokers, further indicating the marked reduction in risk afforded by cessation of smoking.

Lipid-Lowering Drug Therapy

Of the published trials of lipid-lowering therapy, two angiographic trials, the Cholesterol-Lowering Atherosclerosis Study (CLAS I and II) and the recently reported Post-CABG Trial (which incorporated secondary clinical end points) included exclusively patients who had previously undergone bypass surgery. Another recent clinical trial of secondary

---

### TABLE 2. Results From Randomized Trials of Cholesterol-Lowering Drug Therapy in Patients With Previous Coronary Bypass Surgery

<table>
<thead>
<tr>
<th>Study Year (Reference No.)</th>
<th>Treatment</th>
<th>Study Period, y</th>
<th>Baseline Cholesterol, mg/dL</th>
<th>% Change</th>
<th>Angiographic End Points: Saphenous Vein Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>LDL</td>
<td>HDL</td>
</tr>
<tr>
<td>CLAS I 1987 (84) n=162</td>
<td>Colestipol 30 mg+niacin 3-12 mg or placebo</td>
<td>2</td>
<td>246</td>
<td>171</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo, %*</td>
<td>...</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference, %</td>
<td>...</td>
<td>-40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>...</td>
<td>.04</td>
</tr>
<tr>
<td>CLAS II 1990 (85) n=103</td>
<td>Colestipol 30 mg+niacin 3-12 mg or placebo</td>
<td>4</td>
<td>246</td>
<td>171</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo, %*</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference, %</td>
<td>-16</td>
<td>-60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>.33</td>
<td>.006</td>
</tr>
<tr>
<td>Post CABG 1997 (86) n=1351</td>
<td>Lovastatin 76 mg or lovastatin 4 mg</td>
<td>4.3</td>
<td>226</td>
<td>155</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-mg group, %*</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference, %</td>
<td>-31</td>
<td>-52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CARE 1996 (87) n=1091</td>
<td>Pravastatin 40 mg or placebo</td>
<td>5</td>
<td>209</td>
<td>139</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo, %*</td>
<td>21</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference, %</td>
<td>-19</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>.08</td>
<td>...</td>
</tr>
<tr>
<td>Post CABG 1997 (86) n=1351</td>
<td>Lovastatin 76 mg or lovastatin 4 mg</td>
<td>4.3</td>
<td>226</td>
<td>155</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-mg group, %*</td>
<td>15.3</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference, %</td>
<td>-18</td>
<td>-39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>.12</td>
<td>.05</td>
</tr>
</tbody>
</table>

CLAS indicates cholesterol-lowering atherosclerosis study. CLAS II consisted of 103 CLAS I patients followed for a further 2 years; CARE, cholesterol and recurrent events study; Post CABG, post coronary artery bypass graft study.

*Percentage of grafts/patients; †Composite endpoint for the CARE trial was death, MI, PTCA, or CABG, and for the Post CABG trial was death, MI, PTCA, repeat CABG or stroke.
prevention with pravastatin, the Cholesterol and Recurrent Events (CARE) Trial, included a substantial proportion of patients (1091 of 4159 patients; 26.2%) with a history of bypass surgery.87 The results of lipid-lowering drug therapy in surgically revascularized patients in these three trials are summarized in Table 2.

The two most recently reported lipid-lowering trials (CARE and Post CABG) have both underscored the need for an increasingly aggressive approach to cholesterol-lowering in patients with established ischemic heart disease, including those with prior surgical revascularization. In the CARE trial, patients with average levels of total and LDL cholesterol treated with lovastatin for 5 years demonstrated a marked (24%) reduction in the rate of the composite end point of fatal and nonfatal coronary events and the need for myocardial revascularization (P=.003).87

In the Post CABG trial, follow-up angiography performed in 1192 patients at a mean of 4.3 years after recruitment, showed that aggressive lowering of LDL cholesterol with lovastatin reduced the progression of vein graft disease (defined as per patient percentage of grafts with a decrease of 0.6 mm or more in lumen diameter), the rate of vein graft occlusion, and the number of new vein graft lesions, as compared with moderate lowering of LDL cholesterol with lovastatin (Table 2). Patients entered into the Post CABG trial had undergone bypass surgery 1 to 11 years before recruitment: Additional recently-published data from this trial indicate that the aggressive cholesterol-lowering regimen (but not the moderate regimen) afforded equivalent benefits in reducing disease progression irrespective of graft age at initiation of drug therapy.88 While the primary end points in the Post CABG Trial were angiographic, the observed reduction in angiographic disease progression was reflected in a reduction in need for further revascularization in the aggressively treated as compared with the moderately treated group (Table 2).86 Although this latter clinical benefit marginally failed to achieve the prespecified level of statistical significance, the progressive divergence of the revascularization curves in the two groups beyond 2.5 years strongly suggests that a significant difference would be observed with continued therapy (Fig 5).

**Antithrombotic Agents**

**Antiplatelet drugs: Aspirin**

Aspirin at a dose of 325 mg/d or higher, in carefully controlled Veterans Administration (VA) Cooperative Studies, increased vein graft patency at 60 days90 and at 1 year90 after coronary bypass surgery as compared with placebo. The effect of aspirin in improving 1-year vein graft patency in the VA study population was markedly dependent on grafted native vessel diameter: if the grafted vessel diameter was ≥2 mm, aspirin significantly reduced vein graft occlusion over placebo (20.1% versus 32.3%; P=.008); for vein grafts placed to vessels ≥2 mm in diameter, aspirin did not improve patency.90

Available data indicate that aspirin is effective in improving vein graft patency only if commenced no later than one day after surgery.90–91 No data exist on commencing aspirin on the second day after surgery, but the drug is ineffective if started on or after the third postoperative day.91

Sulfinpyrazone, a related drug, has shown inconsistent benefit even when administered within 1 day of surgery.91 Several studies, including the CABADAS trial (prevention of Coronary Artery Bypass graft occlusion by Aspirin, Dipyridamole and Acenocoumarol/phenprocoumon Study) have shown that addition of dipyridamole to aspirin is no more effective than aspirin alone in maintaining graft patency.92 In contrast to the significant benefit of aspirin during the first postoperative year, aspirin 325 mg/d does not improve vein graft patency between 1 and 3 years after bypass surgery.93 This lack of effect of aspirin on graft patency beyond 1 year is consistent with a recognized predominant effect of the drug in offsetting early thrombosis, and also supports findings from a canine model of bypass grafting that aspirin has no effect on intimal hyperplasia or on cholesterol uptake by grafts.94

The reduction in early graft thrombosis with aspirin is unlikely to be primarily a prostaglandin-mediated effect, because the dose of aspirin that almost completely inhibits thromboxane A2 is 20 to 40 mg/d, whereas the dosage which has been definitively shown to improve graft patency is 325 mg/d or higher.95,96 This apparent discrepancy may relate to the observation that platelets subjected to shear forces initiate a hemostatic reaction by releasing von Willebrand factor and ADP, leading to marked thrombin generation and platelet aggregation. Ratnatunga and coworkers97 studied 294 patients 3 months after bypass surgery and observed that 325 mg of aspirin markedly suppressed in vitro shear-induced platelet activation involving thrombin generation, whereas 75 mg of aspirin was associated with significant preservation of shear-induced platelet hyperreactivity.
Of potential clinical relevance is the recently recognized occurrence of aspirin nonresponsiveness in a substantial proportion of patients undergoing bypass surgery. Of 40 consecutive patients who underwent coronary bypass grafting, only 23 (58%) exhibited inhibition of platelet biochemistry and function tests in response to 325 mg of aspirin. In the remaining 17 (42%) patients (aspirin nonresponders), platelet adhesion and platelet 12 hydroxy-eicosatetraenoic acid (12-HETE) synthesis were increased with no prolongation of bleeding time, despite the inhibition of platelet aggregation and thromboxane A2 synthesis. Whether aspirin nonresponsiveness in patients undergoing bypass surgery is as prevalent as this initial small study suggests and whether this nonresponsiveness translates into increased early graft occlusion rates require further study.

Other antiplatelet agents
Indobufen, a reversible inhibitor of platelet cyclo-oxygenase, has been evaluated in two randomized trials after coronary bypass surgery. In the Studio Indobufene nel Bypass Aorto-coronarico (SINBA), composed of 349 patients, indobufen 400 mg was as effective as aspirin 975 mg/d plus dipyridamole 225 mg/d in maintaining graft patency, determined angiographically at 1 year, with a lower incidence of gastrointestinal side effects in the indobufen-treated group. Similarly, in the other trial of 803 patients, indobufen was as effective as aspirin with dipyridamole in preventing vein graft occlusion at 1 year. Indobufen was again better tolerated than aspirin and was associated with less postoperative blood loss, raising the possibility of preoperative administration.

Ticlopidine, a thienopyridine derivative, inhibits platelet aggregation by blocking the interaction between ADP and its platelet receptor. The drug has been studied in two placebo-controlled trials after bypass surgery. In each case a daily dose of 500 mg was administered from the second postoperative day, for 3 and 12 months, respectively, after surgery. In the first trial of 150 patients, vein graft patency at 3 to 8 months after surgery in the ticlopidine-treated group was 92.9% as compared with 78.2% in the placebo-treated group (P<.02). In the second trial of 173 patients, 12 month vein graft patency was 84.1% in the ticlopidine-treated group and 73.9% in placebo-treated patients (P<.01). There are no published comparisons of vein graft patency rates with aspirin versus ticlopidine, or, more importantly, of aspirin versus the combination of aspirin and ticlopidine. On the basis of the efficacy of this latter combination in reducing subacute thrombosis of intracoronary stents, one would anticipate similar synergy between the two drugs in decreasing vein graft thrombosis. One potential disadvantage of ticlopidine is that around 0.8% of patients treated with the drug develop reversible but severe neutropenia: this adverse effect could necessitate discontinuing the drug in the early postoperative weeks, the period during which vein grafts are most vulnerable to thrombotic occlusion. The ticlopidine analogue, clopidogrel, with a minor structural modification, shows a negligible incidence of neutropenia and, in a recently published large multicenter trial, the drug showed modest overall benefit compared with aspirin in improving clinical outcome in patients with atherosclerotic native coronary, cerebrovascular or peripheral vascular disease. Although the possibility exists of a role for clopidogrel as sole antiplatelet therapy or as an adjunct to aspirin in improving early vein graft patency, the drug remains to be evaluated in this latter context.

Oral anticoagulants (coumadin)
In two early placebo-controlled trials of oral anticoagulant therapy in which treatment was commenced 3 to 4 days after bypass surgery and a prothrombin time (PT) ratio of 1.5 to 2.3 was attained, no improvement in graft patency was observed.

In a third placebo-controlled trial in which oral anticoagulation was initiated on days 4 to 7 and a PT ratio in the range 2.2 to 2.7 was attained, oral anticoagulation marginally improved graft patency at 8 weeks (90.4% versus 84.6%; P=.015). Increased bleeding has occurred with oral anticoagulants as compared with placebo, even when therapy is started 3 to 4 days after surgery. Several comparative antithrombotic trials, including CABADAS, have shown that oral anticoagulation administered to attain PT ratios of 2.4 to 4.8 are equivalent, but not superior, to low-dose aspirin with or without dipyridamole in terms of 1-year vein graft patency rates. In the recent Post CABG trial, as part of the 2x2 factorial design, low-dose warfarin or placebo were administered to 1351 patients. Although the target range for the international normalized ratio (INR) was 1.8 to 2.0, the mean INR attained in the warfarin-treated group was only 1.4. Also of note is that although 93% of patients in each group were taking aspirin, the daily dose in 86% of patients was only 81 mg/d. In this study, warfarin was not superior to placebo in influencing rates of disease progression (34% versus 32%; P=.48) or graft occlusion. Reflecting these angiographic outcomes, no differences were observed between warfarin-treated and placebo-treated patients in rates of myocardial infarction (5.0% versus 5.0%) or need for further revascularization (7.8% versus 7.9%). However, trends were observed in the warfarin-treated group toward reductions in total mortality (3.9% versus 5.5%; P=.17) and stroke (1.5% versus 3.0%; P=.15). Although these latter findings did not achieve statistical significance, they may represent true beneficial effects of oral anticoagulation in this setting, since the post CABG trial was underpowered to demonstrate statistically significant clinical benefit. This requires further evaluation.

Current Recommendations and Future Directions for Antithrombotic Prescribing After Coronary Bypass Surgery
On the basis of the cumulative evidence, the current recommendation is to prescribe aspirin alone, in a dose of 325 mg/d, to be commenced 6 hours after surgery or, if initial bleeding prevents this, as soon as possible thereafter. Although aspirin has no discernible effect on vein graft patency beyond 1 year, it is indicated indefinitely because of its clear benefits in patients with native vessel coronary artery disease. Warfarin (coumadin) at any dose is not currently recommended. Newer antiplatelet agents such as thienopyridines are recommended only for patients in whom aspirin is contraindicated, such as in salicylate allergy. If future studies establish aspirin nonresponsiveness to be a clinically important problem in terms of
reduced graft patency, perhaps the use of alternative antiplatelet agents should be extended to this group.

Furthermore, the continuing high incidence of early thrombotic vein graft occlusion with established antiplatelet regimens suggests that, bleeding problems notwithstanding, more potent antithrombotic agents, or combinations of agents (eg, aspirin plus clopidogrel, platelet IIbIIIa receptor antagonists) may be indicated after bypass surgery.

Use of Arterial Grafts
It is a salutary but sobering tenet that the only certain strategy at present for preventing vein graft disease is to avoid the problem by implanting an arterial graft (preferably the internal mammary artery) rather than a venous graft as conduit of choice whenever possible.

Internal Mammary Artery
The left internal mammary artery (IMA) was the first vessel to be used as a coronary bypass graft in man. In February 1964 in Leningrad, Dr Vasili Kolessov performed a sutured end-to-end anastomosis between the left IMA and an obtuse marginal branch of the circumflex coronary artery. Although the IMA initially fell from favor as a result of early, ill-founded concerns regarding low flow rates and technical difficulties in implantation, today it is recognized that selection of the IMA rather than a saphenous vein as the initial conduit is the single most important factor in improved survival, freedom from cardiac events and long-term graft patency after coronary bypass surgery. The favorable effects on mortality and morbidity are observed irrespective of age, gender, or left ventricular function and are particularly evident if the IMA is implanted into a proximally stenosed left anterior descending coronary artery (LAD), in view of the large area of myocardium subtended by this native vessel.

A recently published 15 year survival analysis of all patients in the CASS registry who had undergone first-time bypass grafting showed that patients with IMA grafts (n=749) had a relative mortality risk of 0.73 as compared with patients with exclusively vein grafts (n=4888). This survival advantage increased over the 15-year period, suggesting that initial selection of the IMA is a more important factor in survival than problems appearing long after surgery, such as progression of native coronary disease. Because of the dramatic benefits afforded by the IMA as a conduit, current recommendations are that its use for bypass grafting should be preferred in all but a few specific situations, as recently emphasized by Loop. These situations include patients with radiation-induced atherosclerosis of the IMA, patients with extensive brachiocephalic atherosclerosis, and patients undergoing reoperation who have patent large-diameter atherosclerotic vein grafts, the replacement of which by the smaller-caliber IMA could result in hypoperfusion.

Underlying the unique benefits of IMA grafting is the striking resistance of this conduit to atheroma, with 10 year patency rates well above 90%. The structural and physical properties of the IMA conferring this resistance to atheroma and the comparative properties of the saphenous vein are summarized in Table 3. Of note, compared with saphenous vein grafting, IMA grafting of the LAD is also associated with less native vessel disease progression proximal to the grafted site.

Both the left and right IMA bypass grafts are associated with high patency rates, and the long-term outcome of bilateral IMA grafting appears favorable. The IMA has also been used effectively as a free graft and as a Y graft and, most recently, as a coronary-to-coronary graft, primarily to the right coronary artery. Uncommonly, recurrent ischemia can occur in the territory subtended by an IMA graft. This can take place via several mechanisms. Most frequently this occurs because of development of significant atheroma in the grafted native vessel distal to the anastomotic site. Less commonly, stenosis occurs within the IMA, usually at the distal anastomosis, as a result of intimal hyperplasia, technical errors in performing the anastomosis, or rarely, atheroma. This problem can be treated successfully by balloon angioplasty with good long-term outcome. Another uncommon source of ischemia is subclavian artery stenosis proximal to the origin of a pedicled IMA graft. The resulting “subclavian steal” syndrome, estimated to occur in around 0.5% of patients with IMA grafts, has been treated effectively by a number of percutaneous interventional techniques, including balloon angioplasty, stenting, and directional atherectomy. Very rarely, a large unligated intercostal branch of the IMA graft may give rise to a coronary steal syndrome.

<table>
<thead>
<tr>
<th>TABLE 3. Comparative Anatomic and Physiological Properties of Internal Mammary Artery and Saphenous Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Property</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Anatomic</td>
</tr>
<tr>
<td>Endothelial fenestrations</td>
</tr>
<tr>
<td>Intercellular (IC) processes</td>
</tr>
<tr>
<td>IC junction permeability</td>
</tr>
<tr>
<td>Internal elastic lamina (IEL)</td>
</tr>
<tr>
<td>Heparan sulfate in IEL/media</td>
</tr>
<tr>
<td>Dependence on vasa vasorum</td>
</tr>
<tr>
<td>Valves</td>
</tr>
<tr>
<td>Size match with grafted native vessel</td>
</tr>
<tr>
<td>Resistance to trauma of harvesting</td>
</tr>
<tr>
<td>Physiological</td>
</tr>
<tr>
<td>Flow reserve</td>
</tr>
<tr>
<td>Shear stress</td>
</tr>
<tr>
<td>Nitric oxide/prostacyclin production</td>
</tr>
<tr>
<td>Vasomotor response to thrombin</td>
</tr>
<tr>
<td>Vasoconstrictor sensitivity</td>
</tr>
<tr>
<td>Vasodilator sensitivity</td>
</tr>
<tr>
<td>Basic fibroblast growth factor receptors</td>
</tr>
<tr>
<td>Lipolysis</td>
</tr>
<tr>
<td>Lipid synthesis</td>
</tr>
<tr>
<td>Lipid uptake</td>
</tr>
</tbody>
</table>

motwani and topol
925
This problem has been successfully treated by embolization of the intercostal branch.\textsuperscript{110}

**Other Arterial Grafts**
The profound and sustained benefits afforded by the IMA have given impetus to utilization of other arterial conduits as coronary bypass grafts.

**Right Gastroepiploic Artery**
The right gastroepiploic artery (GEA), a branch of the gastroepiploic artery, was used initially as a Vineberg-type implant in the 1960s. It was first used as a pedicled coronary graft in June 1984 and gained in popularity after reports of 95% patency rates at 5 years.\textsuperscript{111} The patency of the in situ right GEA, which reaches the inferior wall of the heart without tension, appears to be particularly favorable when anastomosed to the posterior descending artery or to the right coronary artery.\textsuperscript{112} Recently published, long-term clinical follow-up of 126 patients who received a right GEA graft during bypass surgery has reported an 87% actuarial survival at 10 years.\textsuperscript{113} Excellent short-term clinical outcome has also been reported in a recent series of 300 patients with simultaneous use of right gastroepiploic and internal mammary arteries.\textsuperscript{114} However, a practical point of note is that the in situ right gastroepiploic artery graft is more difficult to image angiographically than either saphenous vein or IMA grafts.

**Radial Artery**
The radial artery was first used as a free coronary bypass graft by Carpentier more than two decades ago, but with reports of very high early closure rates, this graft fell from favor. Resurgence in use of this conduit has occurred after improved understanding of its marked vasoreactivity, which accounted for the poor early patency rates. Improvements in harvesting and surgical technique that avoid endothelial disruption, and the liberal use of intraoperative papaverine and of perioperative and postoperative calcium channel blockers to overcome graft spasm, have markedly improved early patency rates. Recent angiographic evaluations have reported 95.7% patency at 12 weeks\textsuperscript{115} and 88.9% patency at 11 months.\textsuperscript{116}

In addition to its use as a free graft, the radial artery has been used as a composite graft with the IMA as an inflow conduit\textsuperscript{115,116} and, more recently, also as a coronary-to-coronary graft to the right coronary artery.\textsuperscript{108}

**Inferior Epigastric Artery**
The inferior epigastric artery is increasingly being used as a free or composite graft, primarily to the right coronary or circumflex arteries. Angiographic patency rates of 97% at 11 days and of \(\approx 90\%\) at 8.5 months have been reported.\textsuperscript{117} Mirroring these angiographic patency rates, short- and medium-term survival and freedom from angina appear favorable.\textsuperscript{117} Long-term results are still awaited.

**Minimally Invasive Coronary Artery Bypass Grafting**
The increasing selection of the IMA as conduit of choice for LAD revascularization has given impetus to the development of minimally invasive coronary artery bypass grafting (MICABG). This innovative technique, first proposed by Benetti and colleagues in 1994, does not involve the use of cardiopulmonary bypass, or of a median sternotomy.\textsuperscript{118} Instead, through a small left thoracotomy the LIMA is harvested with or without the aid of a thoracoscope, the pericardium is opened, and the LIMA is grafted to the LAD. Of the increasing number of published series utilizing this technique, the largest series to date was reported by Calafiore and colleagues.\textsuperscript{119} Of 155 patients who underwent LIMA to LAD anastomosis by MICABG (direct anastomosis in 144 patients and interposition of the inferior epigastric artery in 11 patients), 77% were discharged on the second post-operative day. Predischarge LIMA patency rate was 95.5%. Reoperation was performed in nine patients for early graft failure and in two patients for late graft failure. One additional patient with an anastomotic stricture subsequently underwent proximal LAD angioplasty. At a mean follow-up interval of 5.6 months, 143 patients (92.2%) were alive, asymptomatic, and event free.\textsuperscript{110}

At present, single vessel coronary artery disease involving the LAD is the primary indication for MICABG. Wider application of the technique, including right IMA or gastroepiploic artery grafting to the right coronary artery, is currently under evaluation.\textsuperscript{118} MICABG may also have applicability in selected cases of reoperative coronary operation.\textsuperscript{120} Furthermore, recent reports in small series of patients indicate the feasibility of an integrated approach to coronary revascularization, involving LIMA to LAD grafting by MICABG, and percutaneous intervention—as either a staged or simultaneous procedure—to right coronary and circumflex arteries.\textsuperscript{121,122}

**Evolving and Potential Strategies for Prevention of Vein Graft Disease**
Whereas established preventive strategies focus on risk factor modification (eg, lipid-lowering therapy) or attempt to circumvent the problem (use of arterial grafts), improved understanding of the pathogenesis of vein graft disease has stimulated the development of a number of new approaches to counter specific pathogenetic mechanisms that are important in the early evolution of vein graft disease.

**Gene Therapy**
Theoretically, saphenous vein grafts are ideal targets for gene therapy because the explanted veins are available for ex vivo transfer of genetic material before grafting. The initial results of gene transfer using replication-defective adenoviral vectors are favorable. In a porcine jugular vein-to-carotid artery interposition graft model, adenoviral transfection of veins before grafting resulted in high expression of an encoded antiatherogenic gene product, a soluble inhibitory form of vascular cell adhesion molecule-1 (VCAM-1).\textsuperscript{123} Cultured human saphenous veins have recently been transfected successfully with an adenoviral vector encoding bovine endothelial nitric oxide synthase, yielding a marked increase in venous endothelial NO production.\textsuperscript{124} Plasmid-liposome vectors have also effected high levels of gene expression in cultured human saphenous veins.\textsuperscript{125}
Another promising application of gene therapy in vein grafts is the use of antisense oligonucleotides to block the expression of genes encoding cell cycle regulatory proteins in smooth muscle cells. Liposome-mediated transfection of these antisense oligonucleotides into rabbit interposition jugular vein grafts profoundly inhibited medial smooth muscle cell proliferation and vein graft neointimal hyperplasia. These genetically modified grafts have subsequently demonstrated a marked and sustained resistance to diet-induced atherosclerosis. This observation further underscores the importance of neointimal hyperplasia as a prerequisite for development of vein graft atherosclerosis.

Synthetic grafts have also recently been studied as a focus for genetic modulation. Synthetic grafts have thus far proved unsatisfactory for aortocoronary bypass because, in contrast to the large-caliber prosthetic grafts employed successfully in the peripheral vasculature, the small caliber of the conduits in the coronary location has resulted in high rates of thrombotic occlusion. In a recent study attempting to improve patency rates, Dacron vascular grafts were seeded with a monolayer of venous endothelial cells transduced with a retroviral vector encoding human tPA. However, the prominent expression of tPA decreased the adherence of seeded endothelial cells. Thus, future endeavors will require expression of antithrombotic molecules lacking proteolytic activity.

Nitric Oxide Donors
Platelet activation, which occurs immediately after bypass surgery, is an important factor promoting early thrombotic occlusion of vein grafts. This propensity to thrombosis is accentuated by deficient venous endothelial production of NO, which, in addition to its marked vasodilator actions, is a potent inhibitor of platelet activation. S-nitrosothiol is a platelet-selective NO donor that significantly inhibits platelet activation in vivo in both venous and arterial bypass conduits. Such agents may have a future role in improving early graft patency during and after bypass surgery.

Modulation of Growth Factors
Inhibition of bFGF activity significantly reduces neointimal hyperplasia in a rat model of carotid balloon injury. In a similar model, local delivery of vascular endothelial growth factor (VEGF), by promoting rapid re-endothelialization, has also been shown to reduce carotid intimal hyperplasia. Although evidence of the efficacy of these approaches is thus far restricted to arterial injury models, the pathogenetic similarities between arterial and vein graft intimal hyperplasia (and, in the case of bFGF, the very high density of ligand receptors in the grafted vein) indicate that bFGF and VEGF modulation in this latter setting should be evaluated.

Tissue Factor Antagonism
Tissue factor, which initiates the extrinsic coagulation cascade (the major source of thrombin generation in vivo), has been implicated in the pathogenesis of intimal hyperplasia in arterial injury models. In experimental vein grafts, tissue factor protein expression is also increased in the intima for at least 3 days after grafting. This enhanced tissue factor expression colocalizes with areas of polymorphonuclear leukocyte infiltration and precedes temporally the development of intimal hyperplasia. Initial studies have shown that anti-tissue factor antibody significantly decreases infiltration of tissue factor–expressing polymorphs into experimental vein grafts at 28 days. However, thus far, no attenuation of intimal hyperplasia has been observed.

External Stenting
Recognition of the importance of increased wall stress in promoting expression of vascular smooth muscle mitogenic factors and intimal thickening of grafted saphenous veins has prompted the development of external graft stenting to limit this expression. In an established porcine model of saphenous vein–to-carotid artery interposition grafting, application of an external Dacron velour stent before graft implantation reduced subsequent intimal and medial hyperplasia and overall vein wall thickness by up to 70% compared with nonstented vein grafts over a 4-week period (P= .01). Longer-term experimental studies of this technique are currently in progress.

Conclusions
Aortocoronary saphenous vein graft disease is comprised of three distinct but interrelated pathological processes: thrombosis, intimal hyperplasia and atherosclerosis. Early thrombosis is a major cause of vein graft attrition during the first month after bypass surgery, while during the remainder of the first year, intimal hyperplasia forms a template for subsequent atherogenesis, which thereafter predominates. The spectrum of risk factors predisposing to vein graft atherosclerosis and its clinical sequelae is broadly similar to that recognized for native coronary disease. However, the
pathogenic effects of these risk factors are amplified by loss of the anatomic and functional integrity of the endothelium during and after grafting, by inherent deficiencies of the vein as a conduit, and by transposition of the vein into the high-pressure arterial circulation. The clinical impact of saphenous vein graft disease is currently increasing, and future efforts to reverse this trend will involve a multitiered approach focusing on prevention (Table 4). Important elements of this preventive strategy will include: avoidance of early thrombogenic graft occlusion by continued improvements in surgical technique and by the optimal use of the most effective antithrombotic agents, with clearer definition of the relevance of aspirin nonresponsiveness; more intensive risk factor modification, in particular early and aggressive lipid-lowering drug therapy; and, emerging from improved understanding of pathogenesis, the continued development of new potential therapies, such as gene transfer, external stenting, and NO donor administration, which target the disease at an early and fundamental level. An even more important measure at present is to circumvent the problem of vein graft disease whenever possible by the preferential use of the internal mammary arteries as conduits. Furthermore, the future of initial myocardial revascularization will likely involve a continuing increase in application of percutaneous interventional techniques, and of synergy between surgical and percutaneous methods of revascularization, particularly as the intractable problem of vein graft disease comes closer to being solved.

References


100. van der Meer J, Hillege HL, Koosstra GJ, Ascoop CAPL, Pijlsner M, van Gilst WH, Lie KI, for the CABADAS research group. Prevention of one-year vein graft occlusion after aortocoronary bypass surgery: a com-


