Coronary vein graft disease: Pathogenesis and prevention

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Not long after coronary artery bypass grafting surgery was described, several reports presented follow-up angiographic data on large cohorts of patients, demonstrating that approximately one-half of saphenous vein grafts fail within 10 to 15 years of surgery and that graft failure is associated with worse clinical outcomes. Three processes are responsible for vein graft failure. Thrombosis, intimal hyperplasia and accelerated atherosclerosis contribute to graft failure in the acute, subacute and late postoperative periods, respectively. Studies have shown that perioperative antiplatelet therapy can reduce early thrombosis and graft failure. As in native coronaries, intensive lipid lowering can attenuate the process of atherosclerosis in vein grafts. Intimal hyperplasia in the vein graft is thought to be an adaptation of the vein to higher pressures in the arterial circulation. This process is further promoted by the loss of inhibition from the endothelial layer, which is injured during surgery. A new 'no-touch' technique for harvesting grafts may be effective in preventing disruption to the endothelial layer, and subsequent intimal hyperplasia and graft loss. Off-pump surgery and endoscopic vein harvesting, which are known to reduce surgical morbidity, have been shown to be no worse than on-pump surgery and open vein harvesting, respectively, in terms of vein graft patency. Various gene therapies can prevent intimal hyperplasia in animal models, but human data obtained so far have been disappointing. Placing an external stent around a vein graft may reduce tangential wall stress and subsequent intimal hyperplasia.

Key Words: *Coronary artery bypass surgery; Endoscopic vein harvesting; External stenting; Gene therapy; No-touch technique; Off-pump bypass surgery; Vein graft disease*

Coronary artery bypass grafting (CABG) is a highly effective method of relieving signs and symptoms of ischemic heart disease. However, its effectiveness is impeded by the limited life expectancy of saphenous vein grafts, which are the most common types of conduits used. The present paper reviews the studies that established our current understanding of the pathogenesis of saphenous vein graft failure, and strategies that have been shown to improve the lifespan of these grafts (Table 1). Studies cited in the present article were identified through a MEDLINE search and, for the sake of brevity, only frequently cited articles are reviewed here.

PATHOGENESIS AND MODELS OF VEIN GRAFT DISEASE

There are three main causes of vein graft failure. In the early (less than one month) postoperative period, acute thrombosis is the dominant etiology. This is related to technical factors such as small

La pathogénèse et la prévention de la maladie du greffon veineux coronaire

Peu après la description du pontage aortocoronarien, plusieurs rapports ont porté sur les données angiographiques de suivi de vastes cohortes de patients, démontrant qu'environ la moitié des greffons veineux saphènes échouent dans les dix à 15 ans suivant l'opération et que l'échec des greffons s'associe à des issues cliniques encore plus négatives. Trois processus sont responsables de l'échec des greffons veineux. La thrombose, l'hyperplasie intimale et l'athérosclérose accélérée contribuent à l'échec du greffon pendant les périodes postopératoires aiguë, subaiguë et tardive, respectivement. Les études démontrent qu'une thérapie antiplaquettaire périopératoire peut réduire le risque de thrombose précoce et d'échec du greffon. Tout comme dans les artères coronaires originales, une diminution lipidique intensive peut atténuer le processus d'athérosclérose dans les greffons veineux. On pense que l'hyperplasie intimale dans le greffon veineux est une adaptation de la veine à de plus fortes pressions de la circulation artérielle. Ce processus est favorisé par la perte d'inhibition de la couche endothéliale, blessée pendant l'opération. Une nouvelle méthode sans contact de prélèvement du greffon pourrait être efficace pour prévenir la perturbation de la couche endothéliale, l'hyperplasie intimale qui s'ensuit et la perte du greffon. Il est démontré que le pontage à cœur battant et le prélèvement veineux par endoscopie, dont l'effet sur la réduction de la morbidité chirurgicale est connu, ne sont pas plus néfastes que le pontage avec circulation extracorporelle et le prélèvement veineux ouvert, respectivement, pour ce qui est de la perméabilité du greffon veineux. Plusieurs thérapies géniques peuvent prévenir l'hyperplasie intimale dans les modèles animaux, mais les données humaines obtenues jusqu'à présent sont décevantes. L'installation d'une endoprothèse externe autour d'un greffon veineux peut réduire la contrainte tangentielle exercée sur la paroi et l'hyperplasie intimale qui s'ensuit.

size of the target vessel resulting in poor distal runoff, size mismatch between the graft and the target vessel creating turbulent flow, graft ischemia, and disruption of the endothelial layer as a result of mechanical trauma and manual distention. The loss of the endothelial layer can promote platelet adhesion and thrombosis as well as vasospasm resulting from decreased nitric oxide levels. In the subacute period (one to 12 months), intimal hyperplasia is the main etiology. This results from the graft's adaptation to higher arterial pressures and loss of inhibition from the endothelial layer. Smooth muscle cells proliferate and then migrate into the intima, where proliferation continues. During the late period (more than 12 months), atherosclerosis becomes the major reason for graft stenosis and occlusion. As in native coronary arteries, vein graft atheromas can rupture and cause thrombotic occlusion of the graft (1). Vein graft atheromas are more diffuse and concentric, less calcified and have poorly developed or absent fibrous caps (2).

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TABLE 1
Strategies shown to be effective in extending the life of saphenous vein grafts

Intervention	Evidence
Antiplatelet therapy	Shown in randomized human trials to be superior to placebo (17-24)
Aggressive lipid-lowering therapy	Shown in randomized human trials to be superior to placebo or less aggressive lipid-lowering therapy (29-32)
No-touch technique	Shown in randomized human trials to be superior to the traditional technique (35,36)
Off-pump surgery	With an experienced surgeon, no worse than on-pump surgery in terms of graft patency (40-43)
Endoscopic vein harvesting	No worse than traditional technique (44,45)
Gene therapy	Shown to be effective in animal trials and human trials of peripheral bypass. Trial in coronary artery bypass graft patients did not show any benefit (57,58)
External stent	Preliminary data in animal studies indicate benefit in preventing intimal hyperplasia. Human data lacking (59-61)

Zwolak et al (3) transplanted rabbits' jugular veins in the carotid artery circulation. The veins were explanted and examined at 1 h, two weeks, four weeks and 24 weeks. At 1 h, there was loss of endothelium at the sites of anastomosis. Denuded areas were covered with platelets, microthrombi and leukocytes. The endothelium was restored within two weeks, although there was already a large increase in smooth muscle proliferation, which resulted in vessel wall thickening. Maximal wall thickness was reached by 12 weeks. The authors hypothesized that the vessel wall thickening was a response of the vein to the increased arterial pressure. This was based on the observation that the tangential wall stress, calculated as the ratio of lumen radius to wall thickness, is constant across a wide range of arteries in different species. In the transplanted jugular vein, the vessel wall thickened until the above ratio reached the normal value for the carotid artery (3).

Vein graft failure is associated with worse clinical outcomes. Halabi et al (4) identified 1243 patients from the Duke cardiovascular databank who had had CABG surgery between 1986 and 2003, and had a coronary angiogram within 18 months of surgery. Follow-up data were obtained for a median of 6.7 years. The primary end point of death, nonfatal myocardial infarction (MI) or revascularization was reached significantly more often in patients who had critical or occlusive vein graft disease on angiography compared with patients who had noncritical or no vein graft disease. Although it included a large number of patients, the study was limited by being a retrospective analysis (4).

LIFE EXPECTANCY OF VEIN GRAFTS AND RISK FACTORS FOR VEIN GRAFT DISEASE

Not long after the widespread adoption of CABG surgery, it was realized that vein grafts are prone to stenosis and closure. This was confirmed by angiographic data on several large cohorts of patients who had undergone bypass grafting. Loop et al (5) published data on the first 20,524 patients who had undergone CABG at the Cleveland Clinic (Cleveland, Ohio, USA) from 1967 to 1981. The mean time to catheterization was approximately two years. In women, 72.8% of grafts were patent compared with 79.2% in men. Campeau et al (6,7) published angiographic data on a group of 82 patients who were among the first 500 patients to receive CABG at the Montreal Heart Institute (Montreal, Quebec). The yearly occlusion rates were calculated to be 2.1% per year between years 1 and 5 to 7, and 5.2% per year between years 5 to 7 and 10 to 12. Higher low-density lipoprotein (LDL) (apolipoprotein B) and lower high-density lipoprotein (HDL) were associated with vein graft disease progression, but age, hypertension and smoking were not. Grondin et al (8) published data on a cohort of

patients who had undergone CABG from 1968 to 1972. The patency rates at one month, one year and 10 years were 89.1%, 76.4% and 56.3%, respectively. Data from the Coronary Artery Surgery Study (CASS) registry (9) showed 90% patency at 60 days, 82% at 18 months and 82% at five years. Left anterior descending coronary artery grafts had higher patency rates than left circumflex or right coronary artery grafts.

Lytle et al (10) selected a group of patients who had undergone CABG at the Cleveland Clinic and had at least two subsequent angiograms, the first within five years of the operation and the second five years after the operation. Presence of angina and the native coronary artery grafted correlated (left anterior descending correlated better than right coronary or left circumflex) with graft occlusion on the first angiogram. On the second angiogram, increasing postoperative interval, interval MI, angina, diabetes and hyperlipidemia were correlated with graft closure. Therefore, risk factors for atherosclerosis were a factor in late graft closure but not early closure.

Fitzgibbon et al (11-13) reported data from two series of patients who had CABG at the Canadian National Defence Medical Centre (Ottawa, Ontario) and the University of Ottawa Heart Institute (Ottawa). All subjects were men and tended to be relatively young (mean age at surgery was 45 years in the first group and 49 years in the second group). The cumulative occlusion rate in the first group of 353 patients was 8% early after the operation, 13% at one year, 20% at five years, 41% at 7.5 years, 41% at 10 years and 45% at more than 11.5 years. The patency rates for the second group were 88% early after the operation, 81% at one year, 71% at 2.5 years, 75% at five years, 60% at 7.5 years, 60% at 10 years, 49% at 12.5 years and 50% at more than 15 years.

Goldman et al (14) reported data on patency rates of vein grafts from a series of patients who underwent CABG from 1983 to 1988. Patency rates were reported as 95% at one week, 84% at one year, 80% at three years, 69% at six years and 61% at 10 years after the operation. Grafts to the left anterior descending artery had significantly higher patency rates. Larger target vessel size, older age, aspirin use, lower serum cholesterol and better Canadian Cardiovascular Society Functional Class were also associated with higher patency rates. Smoking status and insulin-requiring diabetes were not associated with graft patency (14). More recent reports show that saphenous vein graft occlusion rates have not improved despite our better understanding of its pathophysiology and preventive strategies. In a series of patients who had CABG from 1996 to 2001, the saphenous graft occlusion rate at one year was 13.6% (15). Cho et al (16) reported one- and five-year patency rates of 82.4% and 80.2%, respectively, in patients who had CABG between 1995 and 1997.

Angiographic follow-up studies such as the ones cited above, despite including large numbers of patients, are limited by varying degrees of patient follow-up. Subjects who have occluded grafts may have higher mortality rates and, because angiograms can only be done on living patients, the patency rates may be falsely elevated. On the other hand, patients who have patent grafts will be less symptomatic and are more likely to refuse invasive follow-up angiograms, making the patency rates appear lower.

PREVENTION

Antiplatelet therapy

Chesebro et al (17,18) studied a group of patients undergoing CABG at the Mayo Clinic (Rochester, Minnesota) from 1977 to 1981. All patients received dipyridamole two days before the operation. At 7 h postoperatively, patients were randomly assigned to placebo or aspirin groups. Within one month of the operation, 3% of distal anastomoses in the aspirin group and 10% in the placebo group were occluded. The two groups were similar in blood loss, transfusions and reoperation for bleeding. The benefit of aspirin treatment persisted beyond the early postoperative period. Patients were re-evaluated at a mean of one year after bypass. The rate of new occlusions on the follow-up angiogram was 9% in the aspirin group and 14% in the placebo group.

Goldman et al (19,20) compared four antiplatelet regimens (aspirin 325 mg daily, aspirin 325 mg three times per day, aspirin 325 mg plus dipyridamole 75 mg daily, sulfinpyrazone 367 mg three times per day) started before the operation versus placebo. Early after the operation (mean 60 days), subjects in the three groups receiving aspirin had higher patency than those who received sulfinpyrazone. This benefit was also seen with late (mean 367 days) catheterization. On both examinations, the benefit of aspirin seemed to be limited to grafts to smaller native coronary arteries.

In another study, Goldman et al (21) compared aspirin started the night before surgery versus within 6 h after surgery. At a median of eight days postoperatively, there was no difference between the two groups in vein graft patency, although the patients who received aspirin before the operation had higher rates of bleeding and required transfusions.

The prevention of Coronary Artery Bypass graft occlusion by Aspirin, Dipyridamole, and Acenocoumarol/phenprocoumon Study (CABADAS) (22) demonstrated that the addition of dipyridamole to aspirin does not significantly improve graft patency, although it results in higher chest tube drainage and the need for transfusion.

Although many trials have studied the benefit of clopidogrel in the treatment of stable coronary artery disease or acute coronary syndromes, data on its potential benefit in maintaining graft patency are scant. A study by Ibrahim et al (23) showed a trend toward improved patency with clopidogrel in addition to aspirin alone, but the difference did not reach statistical significance. The ongoing Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial will assess the addition of clopidogrel to aspirin using angiography and intravascular ultrasound one year after the operation (24). Several trials have investigated the use of vitamin K antagonist (VKA) anticoagulants (25-27). Only one study (26), in which oral VKA started after postoperative day 7 was compared with no anticoagulation, showed some improvement from the control group. In the other studies, VKA did not result in improved patency.

In summary, aspirin therapy started within a few hours after surgery is clearly beneficial in preventing early graft thrombosis. Starting aspirin the night before surgery or adding dipyridamole increases the risk of bleeding with no additional benefit in terms of prevention of acute graft failure. The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy (24) recommended starting aspirin 75 mg to 325 mg 6 h after an operation rather than giving aspirin preoperatively. Clopidogrel is recommended for patients who have an allergy to aspirin, or are undergoing CABG for non-ST elevation acute coronary syndrome. A VKA is not recommended for patients who have no other indication for VKAs.

Lipid-lowering therapy

As in atherosclerotic disease of native coronary arteries, vein graft disease seems to be correlated with serum lipid levels, and pharmacological lowering of LDL seems to reduce the incidence of graft occlusion.

In a study of patients with a history of CABG undergoing coronary angiography, Hoff et al (28) found a linear correlation between degree of graft stenosis and the serum lipoprotein(a) level. At approximately the same time, the Cholesterol Lowering Atherosclerosis Study (CLAS) (29,30) assessed the benefits of lowering LDL and raising HDL on angiographic disease progression in vein grafts as well as native coronary arteries. Subjects were placed on colestipol 30 g daily and niacin 3 g to 12 g daily, and were randomly assigned only if they showed significant response to the above regimen. Compared with placebo, the treatment group had a 43% reduction in LDL and a 37% increase in HDL. There was a significant decrease in the formation of new lesions or progression of disease in bypass grafts in the treatment group. New lesion formation in vein grafts was significantly correlated with the combined clinical end point of revascularization, nonfatal MI or cardiac death.

The Post Coronary Artery Graft Trial (31,32) compared a strategy of intensive lipid lowering against moderate lipid-lowering therapy in patients who had undergone CABG one to 11 years before screening. Both groups received lovastatin and, if needed, cholestyramine to reach an LDL target of 60 mg/dL to 85 mg/dL (1.6 mmol/L to 2.2 mmol/L) for the intensive therapy group and 130 mg/dL to 140 mg/dL (3.4 mmol/L to 3.6 mmol/L) for the moderate therapy group. On average, subjects had follow-up angiograms 4.3 years after entering the study. The aggressive strategy was found to lower the percentage of grafts with disease progression per patient and the rate of revascularization. At the end of the study, the aggressive strategy showed a nonsignificant benefit in the combined clinical end point of death from any cause, MI, cerebral vascular accident, CABG or percutaneous coronary intervention. This benefit became statistically significant during the extended study period (31,32). There are no long-term data for newer, more potent statins such as atorvastatin, although it would be reasonable to assume that they would be at least as effective as the older statins in preventing vein graft disease.

Tight glycemic control in diabetics has been shown to be effective in primary and secondary prevention of native coronary atherosclerosis. However, long-term data on the benefit of glycemic control for prolonging vein graft patency are lacking.

Surgical technique

At the time of harvesting, vein grafts are routinely stripped of the adventitial layer and distended with normal saline to overcome spasm. An important cause of graft failure is the trauma on the graft caused by this distention (33). In an experiment in which saphenous veins of pigs were anastomosed to the carotid arteries, some of the veins were distended at 600 mmHg for 30 min before implantation. At one to five weeks, the grafts were explanted and examined. The undistended grafts were 98% covered with endothelium, whereas the distended grafts were only 34% covered. The undistended grafts also had a higher patency rate (34). A new method of harvesting vein grafts, the so-called 'no-touch' technique, whereby the graft is harvested with the surrounding tissue intact and manual distention is avoided, has been described. Tsui et al (35) examined excess samples from harvested saphenous veins from 10 patients undergoing CABG. The distal portion was stripped of its adventitia and distended, whereas the proximal portion was harvested using the no-touch technique. Immunostaining demonstrated a more intact endothelium in the proximal portion, and higher levels of nitric oxide synthase. The no-touch technique was compared with the traditional and an intermediate harvesting technique in a prospective trial (36) that randomly assigned 156 patients to one of the three techniques. In the intermediate group, the vein grafts were harvested without the surrounding tissue; however, papaverine was applied to the vein to avoid its manual distention. The grafts were assessed on angiography at a mean of 18 months. There were significantly more patent grafts in the no-touch group (95.4%) compared with the traditional group (88.9%) and the intermediate group (86.2%) ($P=0.025$).

Compared with on-pump coronary bypass surgery, off-pump coronary artery bypass has been demonstrated to improve postoperative morbidity including neurological impairment, renal damage and myocardial injury. On-pump surgery, however, has the advantage of providing the surgeon with a bloodless and motionless heart, which is optimal for creating vascular anastomoses. Initial reports showed lower vein graft patency and higher rates of subsequent revascularization in patients undergoing off-pump coronary artery bypass (37-39). As surgeons have gained experience with off-pump surgery, this difference has been eliminated. In a study published in 2003, Nathoe et al (40) randomly assigned 265 low-risk patients to on-pump or off-pump surgery. After one year, there was no difference in graft patency (93% versus 91%, respectively) or composite end point of death, MI, stroke or myocardial revascularization. The PRAGUE-4 trial (41) randomly assigned 400 patients to on-pump or off-pump surgery. At one year, the vein graft patency was 59% for on-pump surgeries and 49% for

TABLE 2
Potential targets of gene therapy and their mechanisms of action

Target of therapy or agent	Mechanism of action	Reference(s)
PCNA	Nuclear protein required by DNA polymerase	Morishita et al (46), Mann et al (50)
cdc2 enzyme	Serine/threonine protein kinase	Morishita et al (46), Mann et al (50)
Mithramycin	DNA-binding drug that selectively inhibits genes that have a GC-rich promoter sequence	Chen et al (47)
E2F	Transcription factor involved in cell cycle regulation	Morishita et al (48), Ehsan et al (54)
Endothelial nitric oxide synthase	Produces nitric oxide, an inhibitor of neointimal hyperplasia	von der Leyen et al (49), Kibbe et al (53)
Bcl-x	Regulator of apoptosis	Pollman et al (51)
TIMP-3	Inhibits metalloproteinases, which are promoters of intimal hyperplasia	George et al (52)
CNP	Inhibits growth of vascular smooth muscle cells	Ohno et al (55)
p53	Transcription factor involved in cell cycle regulation	Mayr et al (56)

p53 and bcl-x are names of specific genes. E2F is the name of a transcription factor. CNP C-type natriuretic peptide; GC Guanine-cytosine; PCNA Proliferating cell nuclear antigen; TIMP Tissue inhibitor of metalloproteinases

off-pump surgeries (P not significant). However, because patients undergoing off-pump surgery received fewer grafts, the total number of patent grafts per patient was lower in the off-pump group. The authors attributed the low patency rates to the increasing complexity of the coronary lesions in patients who are currently being referred for bypass surgery. The Surgical Management of Arterial Revascularization Therapies (SMART) (42) randomly assigned 200 patients to on-pump or off-pump surgery. On early angiography, before discharge and at one year, there was no difference in patency rates between the two groups. Khan et al (43) reported data on 104 patients randomly assigned to on-pump or off-pump surgery. There was a higher overall graft patency rate for the on-pump group, which was entirely due to left internal mammary artery or radial artery grafts. There was no difference in patency rates for vein grafts (95% in the on-pump group and 91% in the off-pump group; $P=0.42$) (43).

Endoscopic harvesting of vein grafts has been shown to result in reduced wound complications, earlier postoperative ambulation and improved overall patient satisfaction. Perrault et al (44) randomly assigned 40 patients undergoing CABG to open or endoscopic vein harvesting. On follow-up angiography (mean three months, range one to nine months), there was no difference between the two groups in vein graft patency. In a study by Yun et al (45), 236 patients were randomly assigned to open or endoscopic vein graft harvesting. On angiography at six months, the occlusion rate was 21.7% for grafts harvested endoscopically, and 17.6% for grafts harvested by the open method (P not significant).

Gene therapy

A promising area of research is in gene therapy to prevent the cellular proliferation that leads to intimal hyperplasia and, ultimately, vein graft failure. In animal models, locally delivered gene therapy has prevented intimal hyperplasia in models of arterial balloon injury and venous grafts placed in arterial circulation (46-56) (Table 2).

In the Project of Ex-vivo Vein graft Engineering via Transfection (PREVENT) trial (57), 41 patients undergoing infrainguinal arterial

bypass using vein grafts were randomly assigned to receive grafts treated ex vivo with an oligodeoxynucleotide (ODN) decoy for E2F, a scrambled ODN or saline solution. E2F is an important transcription factor involved in regulation of the cell cycle. Fluorescent microscopy confirmed the successful delivery of ODNs. The subjects were followed for a median of 53 weeks with serial duplex ultrasonography. At 12 months, there were fewer graft occlusions, critical stenoses and revisions in the group treated with the E2F decoy.

The technique described above was subsequently studied in a much larger trial in vein grafts intended for CABG. In the follow-up PREVENT IV trial (58), 3014 patients undergoing CABG were enrolled. Harvested veins were randomly assigned to ex vivo treatment with edifoligide (an E2F decoy), or saline solution placebo at nondistending pressure before grafting. Patients were scheduled for follow-up angiograms 12 to 18 months after the operation. There was no difference in the rate of graft occlusion (41.8% in the edifoligide group versus 41.7% in the placebo group; $P=0.97$). There was also no statistically significant difference in the primary end point of death or vein graft occlusion of 75% or higher, and the composite clinical end point of death, MI or revascularization. Confirming the clinical significance of vein graft failure, major adverse cardiac events occurred more frequently in patients with graft failure (58). For now, gene therapy remains an active area of research but with no apparent benefit in the management of graft disease.

External stent

Stents placed externally around a vein graft at the time of implantation may reduce the tangential stress on the vessel wall and, therefore, prevent disruption of the endothelium and intimal hyperplasia.

Stooker et al (59) placed seven pairs of human saphenous veins harvested using the no-touch technique in a perfusion circuit and perfused them with oxygenated human blood for 60 min at 60 mmHg of nonpulsatile pressure. One-half of the veins were placed inside an external stent before being placed in the circuit. After 60 min, the stented grafts had an intact endothelial layer, whereas the unstented grafts had complete de-endothelialization (59). The above results should be interpreted with caution because, in the operating room, saphenous veins harvested for coronary grafting are not distended in the manner described above.

In an experiment using pig saphenous veins anastomosed into the animals' carotid arteries, external stenting of the saphenous vein resulted in significant inhibition of intimal and medial thickening. The stented grafts also had lower levels of proliferating cell nuclear antigen and platelet-derived growth factor than in the unstented grafts (60,61).

Our understanding of the usefulness of external stenting remains very limited. Further research, including randomized human clinical trials, is clearly needed.

CONCLUSION

The benefits of CABG surgery remain limited by the life expectancy of the most common type of graft, the saphenous vein. Several strategies have been shown to be effective in extending the life of such grafts, such as the use of antiplatelet and lipid-lowering agents, and the avoidance of distention and trauma to the graft during harvesting and implantation. Other strategies, such as gene therapy and external stenting, are still at the experimental stage. Surgical techniques of off-pump surgery and endoscopic harvesting, while improving other outcome benchmarks, are at least no worse than on-pump surgery and open harvesting, respectively, in terms of vein graft patency.

Nearly 40 years after the introduction of bypass surgery, the rate of vein graft failure remains at unacceptably high levels. This may be due to the greater severity of coronary disease in patients who are referred for bypass surgery in the era of percutaneous interventions. It is hoped that the development of newer surgical techniques and more effective medical and gene therapies will significantly prolong the lifespan of vein grafts and help keep patients symptom-free.

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