Editorial

Disconnect Between Vein Graft Failure and Clinical Events After Coronary Artery Bypass Graft Surgery

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The high attrition rate of vein grafts after coronary artery bypass graft (CABG) surgery is well documented. However, the expected clinical events associated with this attrition lag behind those observed in clinical practice. Vein graft patency is complex and multifactorial and can be dependent on technical or patient variables. It is not unusual for these factors to be interrelated. Recurrent angina or an acute event and the need for revascularization remain the most common clinical manifestation of vein graft failure (VGF). In the vast majority of patients, a percutaneous procedure rather than a repeat CABG is the norm. Another important factor in this equation is a patent left internal mammary artery graft to the left anterior descending artery (LAD). The low failure rates of this graft 10 to 20 years after CABG, along with percutaneous interventions, may have contributed to the major decline in the rate of reoperation CABG surgery.

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Novel therapies that may theoretically reduce the incidence of VGF are both attractive and challenging. The question remains, Is it necessary and worth the effort?

The PREVENT IV Study

The PREVENT IV (Project of Ex-Vivo Vein Graft Engineering via Transfection IV) study was an attempt to manipulate the vein graft cells into inhibition of neointimal hyperplasia, which is ultimately responsible for VGF. Edifoligide was transfected into vein graft cells and acted as a decoy to inhibit the E2F transcription factor, which is responsible for upregulation of several genes that mediate mitosis and initiate the cascade of neointimal hyperplasia. More than 3000 patients were randomized to receive edifoligide or placebo. The first 2400 patients were enrolled in the angiographic cohort (12–18 months after randomization). Patients who died before 18 months and without an angiogram were considered to have all grafts occluded. The primary end point was death or VGF (>75% stenosis) at 12 to 18 months. Secondary end points were the composite of major adverse cardiac events, death, myocardial infarction (MI), or repeat revascularization through 5 years. Enrollment was completed in October 2003, and angiographic follow-up was completed in March 2005.1

In this issue of Circulation, Hess and colleagues2 report insights from the PREVENT IV study on VGF after CABG surgery. This is the 11th study published in a major journal reporting results of the PREVENT IV study3–12 and involves the same patients. The angiographic results were analyzed from different clinical angles. The major finding of the PREVENT IV study is that VGF occurs in 42% of CABG patients and in 25% of vein grafts used. This reinforces our knowledge about the fate of vein grafts after CABG. The importance of this study lies in the fact that it is perhaps the only study in a long time that has had solid angiographic proof of VGF rates at 12 to 18 months. Incidentally, edifoligide did not prove efficacious in reducing VGF. Therefore, it was marginalized, and most of the studies on PREVENT IV concentrated on dicing and analyzing data in many different ways. Results were the same. VGF continues to occur. The present study analyzed the data in a sophisticated statistical analysis exploring VGF at the patient and graft levels. After multivariable adjustments, longer surgical duration, endoscopic vein harvesting, poor targets, and postoperative use of clopidogrel were associated with patient-level VGF.

Target Vessel Quality and Surgical Duration

It is no surprise that target vessel size and quality may be intimately related to the longevity of vein grafts. Consequently, longer duration of ischemia and cardiopulmonary bypass time may be a surrogate for the quality of the grafted coronary artery, the quality of the venous conduit, or the experience of the surgeon. A sizable coronary artery free of atherosclerotic disease at the site of the anastomosis takes less time to graft. The other extreme, a small and diffusely diseased artery that may or may not require coronary endarterectomy, will take longer to graft, especially in inexperienced hands. Target vessel quality and size are associated with variable degrees of resistance to blood flow (runoff) and may reduce or increase shear forces on the lumen of the vein graft that is not anatomically designed for artery-level pressures. Consequently, vein graft flow into a good-quality coronary artery mitigates many of the factors responsible for neointimal hyperplasia and ultimately VGF.

Endoscopic Vein Harvest

Enrollment in this study was completed 11 years ago and conducted in 107 centers. At that time, endoscopic vein harvest (EVH) was in its infancy with a wide variation in operator experience. These variations could not be objectively measured and adjusted for in a study that was not designed to look
into method of vein harvest. For example, different operators and centers may or may not give heparin at the time of EVH to prevent intraluminal thrombus formation, and if they did give heparin, the doses were not standard. Since 2003, the technology of EVH has evolved so much that we are now on seventh-generation devices that are undoubtedly superior to those used in this study. In addition, in most US centers, EVH is widely used, and the new generations of physician assistants do not know how to do an open vein harvesting.\textsuperscript{6} It will be interesting to know if any surgeons who are authors of this study have abandoned EVH.

**Antiplatelet Therapy**

Aspirin is currently the recommended antiplatelet therapy for long-term use after CABG. In this study, 20% of patients were on clopidogrel, and those patients had significantly higher rates of VGF. A closer examination is required to decipher this relationship. Patients are on clopidogrel after CABG because either they had sustained a recent acute coronary syndrome (with or without a stent) or they are allergic or resistant to aspirin. In the latter case, clopidogrel would be used as a single antiplatelet therapy as opposed to dual antiplatelet therapy with aspirin. The efficacy of dual antiplatelet therapy in preventing VGF has not been established by large, randomized studies. We believe that a major shortcoming of this study is the absence of the circumstances of why the patients were on clopidogrel and the interaction with statins (only 70% of patients were on statins), which are aggressively used to prevent VGF after CABG.

**Clinical Events After CABG**

Death, MI, and repeat revascularization were the clinical events measured after CABG surgery in the PREVENT IV study. Repeat revascularization with percutaneous coronary intervention or repeat CABG was indicated for recurrent angina or acute coronary syndrome. This should be analyzed separately from protocol angiography—driven revascularization that was not clinically indicated. Of the 2400 patients who were slated to have a study-mandated angiography, <3% died and 3.4% had clinically driven angiography, which accounted for 7.1% of patients with VGF. In the 1829 patients who completed angiography at 12 to 18 months, there was a surge in death, MI, or revascularization in the 14 days after protocol angiography in patients with VGF. Overall 5-year incidence of death, MI, or repeat revascularization occurred in 26% of patients, with death or MI accounting for half. These patients had to be excluded from future analysis. More than twice as many patients with VGF required revascularization compared with those without VGF (10% versus 3.4%). Luckily, they were not close to 42% of VGF in the same patients.\textsuperscript{9,11}

**Repeat Revascularization After CABG**

In the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial (SYNTAX),\textsuperscript{14} patients who had more complex coronary anatomy were categorized by the SYNTAX score. The rate of revascularization at 5 years was 15.5%. The majority of patients with revascularization (13.8%) required percutaneous coronary intervention, and 1.7% had repeat CABG.\textsuperscript{15} Patient characteristics and rates of death, MI, and repeat revascularization were almost identical to the PREVENT IV results.

An analysis of Society of Thoracic Surgeon database from 2000 to 2003 showed that the rate of repeat CABG declined from 6% to 3.4% of the total CABG volume. This is in the setting of increased complexity of patients with a relative risk reduction of 23% in operative mortality. Reasons for this decline are most likely related to available percutaneous options, and most of these patients have a patent left internal mammary artery to LAD.\textsuperscript{16}

In a study from the Cleveland Clinic of 4640 patients who had a patent left internal mammary artery to the LAD but at least 50% stenosis in non-LAD territory grafts, repeat intervention, whether percutaneous or repeat CABG, had no survival benefit compared with medical therapy, reinforcing the premise that a jeopardized LAD territory is most likely to benefit from revascularization to confer a survival benefit.\textsuperscript{17}

**Conclusions**

Vein grafts remain the most commonly used conduits for non-LAD arteries. VGF rates continue to be high, and pharmacological efforts to slow or eliminate pathological vein graft disease have not been successful. We believe that improved results after CABG are multifactorial, including secondary therapeutic prevention measures and the choice of good-quality veins to good-quality targets. The gap between VGF and clinical events is wide, with significant numbers of asymptomatic graft failures. Technology for EVH has improved tremendously, and the learning curve has grown. The impact of VGF warrants re-evaluation. Importantly, a patent left internal mammary artery to the LAD, which was not analyzed in depth in this study, contributes to improved clinical outcomes after CABG.

**Disclosures**

None.

**References**


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