Commentary: Can the Venous Graft External SupporT (VEST) trials bypass surrogate outcomes?

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Coronary artery bypass grafting is the preferred treatment for severe coronary artery disease. Saphenous vein grafts (SVGs) remain the most commonly used conduit despite greater rates of postoperative thrombosis and late graft failure driven by intimal hyperplasia (IH) and atherosclerosis.1 The early European Venous Graft External SupporT (VEST) I-IV trials examined the use of an external stent device aimed at limiting wall stretch, vascular smooth muscle cell proliferation, and IH of SVGs.2 The initial trial found significant 1-year reductions in IH and lumen uniformity, which helped VEST receive Conformité Européenne approval for commercial availability in the European Union. By contrast, the recently published North American VEST Pivotal Trial reported no difference in IH according to intravascular ultrasound (IVUS) between stented and nonstented grafts in the primary analysis, likely related to reduced study power amidst unexpectedly high rates of overall graft occlusion and accordingly IH measurements in only 113 of 203 patients.3 Secondary end points of SVG disease, including Fitzgibbon luminal uniformity, percent stenosis, and Thrombolysis in Myocardial Infarction graft perfusion, were reported but not analyzed. In this issue of the Journal, Goldstein and colleagues4 examined how SVG disease correlates may bridge IH to clinical outcomes in a secondary analysis of the VEST US Pivotal Trial.

The VEST Pivotal Trial used within-patient randomization to compare 406 stented and unstented grafts within 203 participants.3 At 12 months, 74 of 203 (36.5%) patients experienced total graft occlusion of ≥1 conduit. Complete IVUS and angiographic follow-up was available for 284 of 406 (70%) grafts. IH was associated with greater Fitzgibbon score, greater SVG stenosis, and lower Thrombolysis in Myocardial Infarction perfusion. All these correlates, in turn, were associated with a greater rate of major adverse cardiovascular and cerebrovascular events (MACCEs) and repeat revascularization. In multivariable regression models, endoscopic and bridge vein harvesting were associated with increased 12-month SVG occlusion.3

The authors should be commended on a well-conducted secondary analysis that strengthens the validity of IH as the primary study end point, which was shown to correlate with SVG disease and hard clinical end points of MACCE and repeat revascularization. The European trials consistently found VEST to be associated with lower IH but have been critiqued for insufficient evidence linking angiographic outcomes to clinical end points.5,6 The positive association between SVG disease and IH also supports the working theory that luminal changes occur in conjunction with vessel remodeling.1,7 Importantly, identifying endoscopic vein harvesting as a predictor of graft occlusion partially clarifies the excessive graft occlusions observed in the VEST Pivotal Trial, with endoscopically harvested
Randomized Endovenous Graft Prospective (REGROUP) trial found comparable clinical outcomes and reduced leg wound complications associated with endoscopic harvesting at 4.7 years, with 10-year follow-up planned. Nevertheless, their sole use of “expert harvesters” throws into question whether operator skill matters more in ensuring vein graft patency than harvesting method.

Despite early Conformité Européenne approval in Europe, neither the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery nor 2021 American College of Cardiology/American Heart Association revascularization guidelines currently recommend using VEST devices in SVG revascularization. The VEST Pivotal Trial results may deter its approval in the United States by the Food and Drug Administration. Central to the controversy surrounding VEST devices are the unclear benefits in clinically meaningful end points. Previous VEST trials have chosen either angiographic patency or IVUS IH as primary outcomes, and all except VEST IV had short follow-up times. The study of Goldstein and colleagues provides some reassurance that SVG markers can surrogate for IH and adverse outcomes, but its results remain hypothesis-generating. We look to the ongoing VEST EU Registry, which will involve real-world data to assess ischemia-driven revascularization at 5 years. Ultimately, Goldstein and colleagues have conducted an important subanalysis that strengthens the primary angiographic outcome of the VEST Pivotal Trial. However, clear clinical end points are necessary to demonstrate the value of external support devices to SVG patency.

References

SVGs in 74% of patients, compared with 31% of patients in VEST III.

Nevertheless, Goldstein and colleagues could not directly connect VEST devices and clinically significant end points despite finding intermediary links through IH and SVG disease (Figure 1). First, the association between IVUS and SVG disease correlates was determined cross-sectionally; whether luminal changes precipitate vascular smooth muscle cell migration and long-term vessel remodeling remains unknown. The VEST Pivotal Trial’s within-patient randomization is well-suited to compare angiographic outcomes and has been used previously to evaluate radial artery versus SVG stenosis by Yamasaki and colleagues. In conjunction with a small sample size, however, this cannot determine whether supported or non-supported SVGs are ultimately responsible for adverse clinical outcomes. Third, although angiographic and IVUS measurements were taken at 12 months, clinical events were measured from randomization to 3 years. Finally, including nonrandomized grafts in the evaluation of MACCE and repeat revascularization precludes comparisons between SVGs with and without VEST.

There may be value in other avenues of improving SVG patency, such as no-touch SVG harvesting, buffered storage solutions, and arteriovenous composites. Similar to pitfalls of the VEST trials, randomized studies of no-touch versus conventional SVG harvesting have relied on angiographic assessments of SVG patency rather than clinical outcomes. The SWEDEGRAFT study will be the first to examine MACE in no-touch versus conventional SVG, which remains in contention (NCT03501303). Findings from the study of Goldstein and colleagues regarding endoscopic vein harvesting are consistent with early literature; the Project of Ex-vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial recorded greater rates of graft failure and adverse outcomes in patients who underwent endoscopic vein harvesting. A decade later, the

FIGURE 1. Association of saphenous vein graft disease markers with intimal hyperplasia and adverse clinical outcomes. TIMI, Thrombolysis in Myocardial Infarction; VEST, Venous Graft External Support; MACCE, major adverse cardiovascular and cerebrovascular event.


