Saphenous Vein Graft Failure After Coronary Artery Bypass Surgery: Insights From PREVENT IV

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Background—Coronary artery bypass grafting success is limited by vein graft failure (VGF). Understanding the factors associated with VGF may improve patient outcomes.

Methods and Results—We examined 1828 participants in the Project of Ex Vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial undergoing protocol-mandated follow-up angiography 12 to 18 months post–coronary artery bypass grafting or earlier clinically driven angiography. Outcomes included patient- and graft-level angiographic VGF (≥75% stenosis or occlusion). Variables were selected by using Fast False Selection Rate methodology. We examined relationships between variables and VGF in patient- and graft-level models by using logistic regression without and with generalized estimating equations. At 12 to 18 months post–coronary artery bypass grafting, 782 of 1828 (42.8%) patients had VGF, and 1096 of 4343 (25.2%) vein grafts had failed. Demographic and clinical characteristics were similar between patients with and without VGF, although VGF patients had longer surgical times, worse target artery quality, longer graft length, and they more frequently underwent endoscopic vein harvesting. After multivariable adjustment, longer surgical duration (odds ratio per 10-minute increase, 1.05; 95% confidence interval, 1.03–1.07), endoscopic vein harvesting (odds ratio, 1.41; 95% confidence interval, 1.16–1.71), poor target artery quality (odds ratio, 1.43; 95% confidence interval, 1.11–1.84), and postoperative use of clopidogrel or ticlopidine (odds ratio, 1.35; 95% confidence interval, 1.07–1.69) were associated with patient-level VGF. The predicted likelihood of VGF in the graft-level model ranged from 12.1% to 63.6%.

Conclusions—VGF is common and associated with patient and surgical factors. These findings may help identify patients with risk factors for VGF and inform the development of interventions to reduce VGF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00042081.

Key Words: coronary artery bypass • coronary disease • myocardial revascularization

Coronary artery bypass grafting (CABG) is one of the most frequently performed surgical procedures in the United States, with >400,000 procedures performed annually. Although CABG improves survival and symptoms in selected patients, surgical success depends on the continued patency of grafts, and graft failure has been associated with worse outcomes. Saphenous vein grafts remain the most widely used conduit during CABG, and the rates of vein graft failure (VGF) during the first 12 to 18 months after surgery have been reported to be as high as 25%. Many studies have examined the factors associated with VGF and have inconsistently reported associations between multiple clinical and surgical characteristics and VGF. These previous efforts have been limited by the absence of systematic angiographic follow-up. In addition, the results from these studies may be outdated, given the advances in surgical techniques and adjunctive medical therapies that could impact graft failure. We therefore sought to examine the factors associated with VGF assessed by coronary angiography 12 to 18 months after CABG by using data from the Project of Ex Vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial.

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Methods

Data Source and Patient Population

We used data from the PREVENT IV trial (clinicaltrials.gov: NCT00042081), the design and results of which have been previously described. In brief, PREVENT IV was a phase 3 randomized, double-blind, placebo-controlled trial of ex vivo vein graft treatment with edofoligide in patients undergoing primary CABG with ≥2 planned vein grafts. A total of 3014 patients were enrolled between August 2002 and October 2003 at 107 centers across the United States, the first 2400 of whom were scheduled for follow-up angiography between 12 to 18 months after CABG. The PREVENT IV protocol was approved by the institutional review boards of all participating sites, and all enrolled patients provided written informed consent.

We included patients in the angiographic cohort who were scheduled to undergo follow-up angiography 12 to 18 months after the index CABG (n=2400). Patients in the angiographic cohort who had VGF documented during earlier angiography for clinical indications were excluded. We excluded patients who did not undergo angiographic follow-up (n=477), who received only arterial grafts (n=4), or who died before their 12- to 18-month repeat angiogram (n=91). Our final analysis population consisted of 1828 patients enrolled at 100 sites (Figure 1).

Definitions and Outcomes

VGF was defined as ≥75% stenosis or occlusion detected at follow-up angiography 12 to 18 months after CABG or earlier angiography performed for clinical indications. All angiograms were analyzed at a core laboratory (PERFUSE Angiographic Core Laboratory, Boston, MA). For grafts with multiple distal anastomoses, failure of any component was considered VGF. Outcomes for our analyses were defined as failure of ≥1 vein grafts (patient-level angiographic VGF) and graft-level angiographic VGF.

Statistical Analysis

Baseline patient and procedure characteristics were examined according to patient-level absence or presence of VGF at 12 to 18 months post-CABG. Continuous variables were summarized by using medians and interquartile ranges, whereas categorical variables were presented as frequencies and percentages. Comparisons within continuous and categorical variable groups were performed by using the Wilcoxon 2-sample test and the χ² test, respectively. We analyzed surgical features at both the patient and graft levels. When describing patient-level characteristics, we used the worst status to describe procedure characteristics for patients with multiple vein grafts. The following hierarchies (worst status listed first) were used: target artery quality=poor, fair, good; graft quality=poor, fair, good; distal connection technique=nonsuture, suture; graft length=longest measurement; graft source=arm vein, lesser saphenous vein, greater saphenous vein; vein harvest technique=endoscopic, open; and use of grafts with multiple distal anastomoses=yes, no.

We developed patient- and graft-level models to determine the factors associated with VGF. For the main analysis, patient-level variables were created by assessing graft-level data for each patient and, for patients with multiple grafts, determining the worst status for each characteristic among all grafts. We also performed a secondary analysis to examine the graft-level variables associated with VGF. For both models, variables associated with VGF were selected by using Fast False Selection Rate. Fast False Selection Rate is a conservative variable selection method that accounts for the percentage of variables incorrectly identified as associated with the outcome of interest. Logistic regression models were then fit using the chosen variables to estimate the association of each factor with VGF and odds ratios (ORs) with associated 95% confidence intervals (CIs) were reported. For graft-level analyses, to account for the correlation among multiple grafts within the same patient, generalized estimating equations were used to fit a generalized linear logistic model that allows for an exchangeable correlation matrix between grafts within a single patient.

The following candidate variables were chosen based on clinical judgment and considered for inclusion in both patient- and graft-level models: age, female sex, weight, race, smoking status, chronic lung disease, hypertension, dyslipidemia, previous myocardial infarction, previous percutaneous coronary intervention, previous cancer, history of liver disease, peripheral artery disease, cerebrovascular disease, previous congestive heart failure, current New York Heart Association class, diabetes mellitus (no history, noninsulin therapy, insulin therapy), renal failure, atrial fibrillation/flutter, ejection fraction, type of CABG procedure (emergent/salvage, urgent, elective), use of cardiopulmonary bypass, cardiopulmonary bypass time, aortic cross-clamp time, surgical time, graft source (greater saphenous, lesser saphenous), vein harvest technique (endoscopic, open), graft quality, maximum stenosis of target vessel (<75%, ≥75%), target artery quality, proximal anastomosis connection technique (suture, nonsuture), graft length, and use of grafts with multiple distal anastomoses. For both patient- and graft-level models, linear splines were used to determine appropriate knot points for the following nonlinear variables (see online-only Data Supplement for knot points): aortic cross-clamp time, ejection fraction, graft length (patient-level model only), and cardiopulmonary bypass time (graft-level model only). Significant (P<0.1) levels were then included as candidate variables (see online-only Data Supplement). We hypothesized that the chronic use of certain medications might be associated with VGF. In PREVENT IV, data regarding medication use were collected at the discrete time points of baseline, discharge, 30 days, and 1 year. We chose to examine 30-day medication use as covariates, because these were thought to best represent chronic postoperative use following the initial surgery. However, because medication use at 30 days is a postbaseline variable, it was included in models as a sensitivity analyses. The rates of missingness for data in our models were ≤1.5%, and no imputation was performed for missing data. Multivariable models were derived from complete cases. For the Fast False Selection Rate method, the desired False Selection Rate was set to 0.05. All analyses were performed at the Duke Clinical Research Institute with the use of SAS version 9.2 (SAS Institute, Cary, NC).

Figure 1. Flowchart of patient selection for the final analysis population.
### Results

**Patient and Procedure Characteristics**

Among a total of 1828 patients included in our study, 782 (42.8%) had VGF at 12 to 18 months after CABG. At the graft level, 1096 (25.2%) of the 4343 grafts placed during the index CABG had failed at 12 to 18 months after CABG. Demographic characteristics and comorbid conditions were similar between patients with and without VGF with the exception of cerebrovascular disease, which was more prevalent among patients with VGF (Table 1).

#### Table 1. Baseline Patient Characteristics According to the Presence or Absence of VGF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With VGF (n=782)</th>
<th>Without VGF (n=1046)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>63.0 (55.0–69.0)</td>
<td>63.0 (55.0–70.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>158 (20.2)</td>
<td>184 (17.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>88.7 (77.0–100.0)</td>
<td>88.0 (78.0–100.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Race: white</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>701 (89.6)</td>
<td>954 (91.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>AF/flutter</td>
<td>54 (6.9)</td>
<td>60 (5.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cancer</td>
<td>72 (9.2)</td>
<td>77 (7.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of CHF</td>
<td>52 (6.6)</td>
<td>69 (6.6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>489 (62.5)</td>
<td>678 (64.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, no current treatment</td>
<td>14 (1.8)</td>
<td>23 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, insulin treatment</td>
<td>85 (10.9)</td>
<td>77 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, noninsulin treatment</td>
<td>194 (24.8)</td>
<td>267 (25.6)</td>
<td></td>
</tr>
<tr>
<td>EF, median (IQR), %</td>
<td>50.0 (40.0–60.0)</td>
<td>52.5 (43.0–60.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>169 (21.6)</td>
<td>254 (24.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>574 (73.4)</td>
<td>760 (72.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>History of liver disease</td>
<td>16 (2.0)</td>
<td>17 (1.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>101 (12.9)</td>
<td>146 (14.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>I</td>
<td>312 (40.4)</td>
<td>427 (41.1)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>271 (35.1)</td>
<td>353 (33.9)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>131 (17.0)</td>
<td>177 (17.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>58 (7.5)</td>
<td>83 (8.0)</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>87 (11.1)</td>
<td>114 (10.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>History of renal failure</td>
<td>6 (0.8)</td>
<td>17 (1.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Never</td>
<td>257 (32.9)</td>
<td>339 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>345 (44.1)</td>
<td>483 (46.2)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>180 (23.0)</td>
<td>224 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>343 (43.9)</td>
<td>432 (41.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>220 (28.1)</td>
<td>279 (26.7)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data presented as n (%), unless otherwise indicated. AF indicates atrial fibrillation; CHF, congestive heart failure; EF, ejection fraction; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and VGF, vein graft failure.

Patient-level CABG procedure characteristics among patients with and without VGF are shown in Table 2. In comparison with patients without VGF, those with VGF had longer surgical and cross-clamp times and worse target artery quality. Patients with VGF also more frequently underwent endoscopic versus open vein graft harvest and had slightly longer graft length than patients without VGF. At 30 days after the index CABG, patients with subsequent VGF were more frequently taking clopidogrel or ticlopidine (26.1% versus 19.2%, P=0.001) and had similar use of warfarin (9.1% versus 8.5%, P=0.66) and statins (74.6% versus 74.9%, P=0.88) than patients who did not have subsequent VGF.

#### Factors Associated With VGF

We first examined patient-level factors associated with VGF at 12 to 18 months after CABG. Longer duration of surgery (OR per 10-minute increase, 1.05; 95% CI, 1.03–1.07; P<0.01), endoscopic vein graft harvest technique (OR, 1.44; 95% CI, 1.19–1.75; P<0.01), and poor target artery quality (OR, 1.45; 95% CI, 1.13–1.87; P<0.01) were significantly associated with VGF. Adding medications continued at 30 days after CABG to the variable selection model revealed that the use of clopidogrel or ticlopidine was significantly associated with VGF (OR, 1.35; 95% CI, 1.07–1.69; P=0.01); addition of clopidogrel or ticlopidine to the model did not substantially change the relationship between the other significant predictors and VGF (Table 3). Goodness of fit of the model as measured by the Hosmer-Lemeshow statistic indicated that the model fits the data well (P=0.85). The C statistic for the model was 0.61. Next, we assessed the relationship of graft-level variables with VGF (Table 4). Factors that were significantly associated with per-graft VGF (Table 4) included fair or poor target artery quality (OR, 1.31; 95% CI, 1.11–1.56; P<0.01, OR, 2.34; 95% CI, 1.89–2.91; P<0.01, respectively), longer duration of surgery (OR per 10-minute increase, 1.04; 95% CI, 1.02–1.05; P<0.01), endoscopic vein harvest technique (OR, 1.37; 95% CI, 1.16–1.62; P<0.01), and history of cerebrovascular disease (OR, 1.39; 95% CI, 1.06–1.81; P=0.02). After including 30-day medication use, clopidogrel or ticlopidine use was again associated with VGF (OR, 1.30; 95% CI, 1.07–1.58; P<0.01).

#### Distribution of Predicted VGF Risk

We examined the distribution of predicted VGF risk by using the full (including 30-day medication use) graft-level model of VGF. Predicted probability of VGF at 12 to 18 months post-CABG ranged from a low of 12.1% to a high of 63.6%. The median predicted risk of VGF among our patient cohort was 23.4% (interquartile range, 19.5%–29.2%; Figure 2).

#### Discussion

In this analysis from PREVENT IV that included >1800 patients, >4300 implanted vein grafts, and systematic 12- to 18-month angiographic follow-up, we found that longer duration of surgery, endoscopic vein graft harvesting, poor target artery quality, and the use of clopidogrel or ticlopidine at 30 days post-CABG were factors associated with VGF in both patient-level and graft-level models. The broad range of predicted VGF using our graft-level model (12.1%–63.6%) suggests that VGF is prevalent, and, hence, these data may be clinically useful to inform the efforts to reduce VGF.
Table 2. Baseline Procedural Characteristics at the Patient Level According to the Presence or Absence of VGF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With VGF (n=782)</th>
<th>Without VGF (n=1046)</th>
<th>( \chi^2 ) OR 95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol angiography only</td>
<td>655 (83.8)</td>
<td>1002 (95.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early angiography only</td>
<td>64 (8.2)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early and per protocol angiographies</td>
<td>64 (8.1)</td>
<td>44 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum stenosis of any target vessel ≥75%</td>
<td>790 (72.3)</td>
<td>2317 (71.5)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Endoscopic vein harvest technique</td>
<td>468 (60.1)</td>
<td>531 (50.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any use of composite graft</td>
<td>286 (36.6)</td>
<td>344 (32.9)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Longest graft length, median (IQR), cm</td>
<td>17.0 (14.3–19.3)</td>
<td>16.0 (14.0–19.0)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Any proximal (nonsuture)</td>
<td>21 (2.7)</td>
<td>19 (1.8)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Any distal (nonsuture)</td>
<td>23 (2.9)</td>
<td>27 (2.6)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Graft source*</td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Arm vein</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesser saphenous</td>
<td>12 (1.5)</td>
<td>22 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater saphenous</td>
<td>770 (98.5)</td>
<td>1022 (97.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst target artery quality</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>308 (39.4)</td>
<td>484 (46.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>281 (36.0)</td>
<td>363 (34.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>192 (24.6)</td>
<td>198 (18.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst graft quality</td>
<td></td>
<td></td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>537 (68.7)</td>
<td>764 (73.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>206 (26.3)</td>
<td>237 (22.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>39 (5.0)</td>
<td>44 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of cardiopulmonary bypass</td>
<td>617 (78.9)</td>
<td>825 (78.9)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Pump time, median (IQR), min</td>
<td>95.0 (62.0–123.0)</td>
<td>86.0 (51.0–111.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Cross-clamp time, median (IQR), min</td>
<td>60.0 (33.0–78.0)</td>
<td>53.0 (30.0–72.0)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Surgical time, median (IQR), min</td>
<td>240.0 (201.0–284.0)</td>
<td>221.0 (186.0–261.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Type of procedure</td>
<td></td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Emergent/salvage</td>
<td>20 (2.6)</td>
<td>32 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent</td>
<td>373 (47.7)</td>
<td>480 (45.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>389 (49.7)</td>
<td>533 (51.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as \( n \) (%), unless otherwise indicated. IQR indicates interquartile range; and VGF, vein graft failure.

*For patients with multiple graft sources, the worst source according to the following hierarchy was used (worst status listed first): arm vein, lesser saphenous vein, greater saphenous vein.

Table 3. Factors Associated With Patient-Level VGF

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \chi^2 )</th>
<th>OR 95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (per 10-min increase)</td>
<td>34.66</td>
<td>1.05 1.03–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endoscopic harvest technique (vs open)</td>
<td>14.07</td>
<td>1.44 1.19–1.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Worst target artery quality (vs good)</td>
<td>7.32</td>
<td>1.24 1.00–1.53</td>
<td>0.05</td>
</tr>
<tr>
<td>Poor</td>
<td>8.35</td>
<td>1.45 1.13–1.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Including 30-day medications</td>
<td>32.51</td>
<td>1.05 1.03–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endoscopic harvest technique (vs open)</td>
<td>12.16</td>
<td>1.41 1.16–1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worst target artery quality (vs good)</td>
<td>3.13</td>
<td>1.22 0.98–1.51</td>
<td>0.08</td>
</tr>
<tr>
<td>Poor</td>
<td>7.55</td>
<td>1.43 1.11–1.84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine use</td>
<td>6.62</td>
<td>1.35 1.07–1.69</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and VGF, vein graft failure.

*1817 patients with nonmissing covariates were included in the without 30-day medications model, and 1812 patients were included in the 30-day medications model.

Interest in understanding the factors associated with VGF after CABG has been longstanding, but previous efforts have been limited. Previous studies have consistently reported 1-year VGF rates of 10% to 20%, with another 5% to 10% of vein grafts failing between 1 and 5 years after CABG. These studies have identified patient characteristics, including younger age, female sex, previous heart failure or low ejection fraction, and increased serum cholesterol, as predictors of VGF. Surgical factors, including temperature of graft solution, have also been identified as predictive of VGF. Importantly, these analyses were based on data from patients undergoing CABG several decades ago, before the widespread use of antiplatelet therapy and the introduction of newer surgical CABG techniques. Some previous reports were also based on single-center studies, reducing the generalizability of their results, or analyzed data at either the patient or graft level, which may account for some of the inconsistency in previous findings. Furthermore, a number of previous studies examined patients undergoing clinically driven coronary angiography, which may underestimate the rate and influence of factors associated with VGF.

Our study extends knowledge in the field in several ways. First, this analysis represents one of the largest analyses of factors associated with VGF after CABG that includes data from >100 sites. Second, our study included patients undergoing angiography for clinical reasons, and relatively complete, protocol-mandated follow-up angiography, as well, allowing for a more unbiased assessment of VGF and the factors associated with it. Third, our analysis was based on data representing more contemporary practice and was strengthened by the detailed clinical and procedural data that were collected for PREVENT IV. Finally, whereas previous studies have
assessed VGF at either the graft or patient level, we examined both, because each provides useful and potentially different information. We found that the factors associated with VGF in patient- and graft-level models were almost identical.

We found a number of surgical factors that were associated with VGF. Pathological studies have demonstrated that atherosclerosis is the main etiology of late (>12 months) VGF, whereas early (<1 month) and subacute (≤12 months) graft failure is due to thrombosis, surgical technical errors, and intimal hyperplasia. Intraoperative processes of vein graft harvesting, graft manipulation, and graft implantation can all lead to endothelial dysfunction, inflammation, and ultimately thrombosis and graft occlusion. Accordingly, there is mechanistic feasibility to explain our study results. Longer duration of surgery may reflect technical difficulty, thus contributing to the risk of VGF. Endoscopic vein graft harvesting, although less invasive than open vein graft harvesting, can damage vein graft endothelium, causing inflammation and thrombosis with early graft failure or increased intimal hyperplasia and subacute VGF. Observational data regarding the benefits of endoscopic vein harvesting are mixed, with some studies reporting associations with VGF and worse outcomes, whereas others have not confirmed these findings. Definitively determining whether endoscopic graft harvesting is associated with VGF will require a prospective randomized clinical study. The Randomized Endo-Vein Graft Prospective (REGROUP) Trial (clinicaltrials.gov: NCT01850082), which is currently under development, will provide important insight into this topic.

We also found that poor target artery quality was associated with VGF. In PREVENT IV, the assessments of target artery quality were based on qualitative surgeon judgment and not systematic classification. However, this qualitative rating likely incorporates the elements of smaller vessel diameter that might reflect challenging surgical anatomy and poor distal runoff, which has been previously associated with VGF.

Table 4. Factors Associated With Graft-Level VGF

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without 30-day medications*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (per 10-min increase)</td>
<td>2.30 (1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endoscopic harvest technique (vs open)</td>
<td>1.37 (1.16–1.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target artery quality (vs good)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>1.11–1.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Poor</td>
<td>1.10–1.55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1.88–2.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>1.11–1.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine use</td>
<td>1.07–1.58</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and VGF, vein graft failure.

Figure 2. Distribution of predicted VGF risk. Shown is the distribution of predicted risk of VGF by the use of the full (including 30-day medication use) graft-level VGF model among the patient cohort. Listed above each bar is the observed probability of VGF. VGF indicates vein graft failure.

Two of the factors significantly associated with VGF in our analyses were not related to the surgical procedure. The first was a clinical history of cerebrovascular disease, which was associated with VGF in the graft-level model. Cerebrovascular disease may represent a marker of both more advanced vascular disease and also poor target vessel distal runoff. We also found that the use of clopidogrel or ticlopidine at 30 days was associated with an increased risk of VGF. Given the pathological contribution of thrombosis to early VGF, antiplatelet therapy would be expected to reduce VGF, and randomized data support the use of aspirin to reduce graft failure. In this study, because the use of antiplatelet therapy was not randomized, we hypothesize that the relationship between antiplatelet therapy and VGF is likely due to confounding. Data to support the use of clopidogrel to improve early venous graft patency after CABG are limited, and clopidogrel is more frequently prescribed to patients with acute coronary syndrome, patients undergoing off-pump CABG, or patients with extensive coronary artery disease.

In our study, the majority of VGF events were clinically silent. Only 7.1% of the patients with VGF had VGF identified during early repeat angiography for clinical indications. However, studies have demonstrated that VGF identified either during clinically driven or routine follow-up angiography is associated with significant morbidity. Recent research efforts to date have focused on a multifaceted approach to prevent VGF, including modifications in patient behavior, especially smoking cessation, and exploration of optimal postoperative antiplatelet regimens, because a large proportion of CABG patients are resistant to aspirin. Given the wide range of predicted VGF risk of our model, these data might help to identify patients at higher risk for VGF who might be considered for CABG with nonvein graft conduits and who should be followed more closely for post-CABG VGF events. However, some of the factors associated with VGF in our study are nonmodifiable, suggesting that the greatest use of our data may be to help direct further research into strategies to prevent VGF. The high rate of VGF also emphasizes the importance of
investigational surgical techniques to reduce vein graft injury, such as external vein graft support through either stenting or fibrin glue, exploration of novel gene-based molecular therapies to reduce VGF, and the development of synthetic, nonvein graft conduits.15

Limitations
This is a retrospective, post hoc analysis. We assessed VGF at routine angiography 12 to 18 months after CABG, and the predictors of VGF may change over time. We were not able to assess VGF in patients who died before angiography or who did not return for protocol-mandated angiography and have excluded these patients from the analysis. We chose to study VGF and did not include arterial conduits in our analysis. The factors associated with arterial graft failure may differ.16,20,42 Some other factors that have previously been associated with vein graft patency were not collected in PREVENT IV.11,28,30,35 PREVENT IV only included patients undergoing first-time CABG, and the vein graft–handling techniques and pressurized delivery system used in PREVENT IV were unique to the trial. Although our models fit the data well ( Hosmer-Lemeshow P=0.85), there was low discriminatory power ( C statistic, 0.61). We also included the use of clopidogrel and ticlopidine in sensitivity analyses, although these were postbaseline variables that might be associated with non-VGF factors. We were not able to account for clustering by specific surgeon, because these data were not available. Finally, it should be recognized that both the study timeframe and identification of VGF based on routine angiography impacted the selection of collected data elements, and strategies to reduce VGF have evolved since the time of this study14; all of these factors may limit the generalizability of our results.

Conclusions
VGF is common and associated with both patient and surgical factors including poor target artery quality, longer duration of surgery, use of endoscopic vein harvesting, use of clopidogrel or ticlopidine, and cerebrovascular disease. These data may be useful in identifying patients with risk factors for VGF and to inform the development of strategies to prevent VGF. Further investigation of VGF should be pursued in contemporary data sets.

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References
Clinical Perspective

Coronary artery bypass grafting is one of the most frequently performed surgical procedures in the United States. Although coronary artery bypass grafting improves survival and symptoms in selected patients, surgical success depends on the continued patency of grafts, and graft failure has been associated with worse outcomes. Saphenous vein grafts remain the most widely used conduit during coronary artery bypass grafting, and the rates of vein graft failure (VGF) during the first 12 to 18 months after surgery have been reported to be as high as 25%. In this analysis from the Project of Ex Vivo Vein Graft Engineering via Transsection IV (PREVENT IV) trial, we examined >4300 implanted vein grafts in >1800 patients undergoing systematic 12- to 18-month angiographic follow-up. At 12 to 18 months post–coronary artery bypass grafting, 782 of 1828 (42.8%) patients had VGF, and 1096 of 4343 (25.2%) vein grafts had failed. We found that mainly surgical factors, including longer duration of surgery, endoscopic vein harvesting, and poor target artery quality, and the use of clopidogrel or ticlopidine at 30 days postoperatively, as well, were associated with VGF in both adjusted patient-level and graft-level models. These data may be useful in identifying patients at higher risk for VGF and to inform the development of strategies to prevent VGF.
Saphenous Vein Graft Failure After Coronary Artery Bypass Surgery: Insights From PREVENT IV

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Knot point selection for non-linear variables encountered during model variable selection

Patient-level model

The following variables were found to be non-linear: aorta cross-clamp time (acctime), pre-operative ejection fraction (ef), and longest graft length (pglen). Each one was split into 3 linear pieces with the cutoff points chosen appropriately. The definition for each spline follows:

\[
\begin{align*}
\text{acctime}_{\text{low}} & = \begin{cases} 
\text{acctime} & \text{if acctime} \leq 45 \\
45 & \text{if acctime} > 45 \\
45 & \text{if acctime} < 45 
\end{cases} \\
\text{acctime}_{\text{mid}} & = \begin{cases} 
\text{acctime} & \text{if } 45 \leq \text{acctime} \leq 95 \\
95 & \text{if acctime} > 95 \\
95 & \text{if acctime} < 95 
\end{cases} \\
\text{acctime}_{\text{high}} & = \begin{cases} 
\text{acctime} & \text{if acctime} \geq 95 
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{ef}_{\text{low}} & = \begin{cases} 
\text{ef} & \text{if ef} \leq 50 \\
50 & \text{if ef} > 50 \\
50 & \text{if ef} < 50 
\end{cases} \\
\text{ef}_{\text{mid}} & = \begin{cases} 
\text{ef} & \text{if } 50 \leq \text{ef} \leq 60 \\
60 & \text{if ef} > 60 \\
60 & \text{if ef} < 60 
\end{cases} \\
\text{ef}_{\text{high}} & = \begin{cases} 
\text{ef} & \text{if ef} \geq 60 
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{pglen}_{\text{low}} & = \begin{cases} 
\text{pglen} & \text{if pglen} \leq 10 \\
10 & \text{if pglen} > 10 \\
10 & \text{if pglen} < 10 
\end{cases} \\
\text{pglen}_{\text{mid}} & = \begin{cases} 
\text{pglen} & \text{if } 10 \leq \text{pglen} \leq 20 \\
20 & \text{if pglen} > 20 
\end{cases} \\
\text{pglen}_{\text{high}} & = \begin{cases} 
\text{pglen} & \text{if pglen} \geq 20 
\end{cases}
\end{align*}
\]

We entered each variable if it was significant (<0.1) in a logistic regression model including only the other levels of the variable. The variables included in our model were acctime_{low}, acctime_{mid}, ef_{mid}, ef_{high}, and pglen_{mid}. Variables were allowed to enter the model separately.
Graft-level model

The following variables were found to be non-linear: aorta cross-clamp time (acctime), pre-operative ejection fraction (ef), and time on bypass pump in minutes (pumptime). Acctime and ef were split into 3 linear pieces with 2 cutoffs, while pumptime was split into 2 linear pieces with 1 cutoff. The definition for each spline follows:

\[
\begin{align*}
\text{acctime}_{\text{low}} &= \begin{cases} 
\text{acctime} & \text{if acctime} \leq 50 \\
50 & \text{if acctime} > 50 \\
50 & \text{if acctime} < 50 
\end{cases} \\
\text{acctime}_{\text{mid}} &= \begin{cases} 
\text{acctime} & \text{if 50} \leq \text{acctime} \leq 90 \\
90 & \text{if acctime} > 90 \\
90 & \text{if acctime} < 90 
\end{cases} \\
\text{acctime}_{\text{high}} &= \begin{cases} 
\text{acctime} & \text{if acctime} \geq 90 
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{ef}_{\text{low}} &= \begin{cases} 
\text{ef} & \text{if ef} \leq 50 \\
50 & \text{if ef} > 50 \\
50 & \text{if ef} < 50 
\end{cases} \\
\text{ef}_{\text{mid}} &= \begin{cases} 
\text{ef} & \text{if 50} \leq \text{ef} \leq 60 \\
60 & \text{if ef} > 60 
\end{cases} \\
\text{ef}_{\text{high}} &= \begin{cases} 
60 & \text{if ef} < 60 \\
\text{ef} & \text{if ef} \geq 60 
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\text{pumptime}_{\text{low}} &= \begin{cases} 
\text{pumptime} & \text{if pumptime} \leq 80 \\
80 & \text{if pumptime} > 80 
\end{cases} \\
\text{pumptime}_{\text{high}} &= \begin{cases} 
\text{pumptime} & \text{if pumptime} \geq 80 
\end{cases}
\end{align*}
\]

We entered each variable if it was significant (<0.1) in a logistic regression model including only the other levels of the variable. Variables included in our model were acctime_low, acctime_mid, ef_low, ef_mid, ef_high, and pumptime_high. Variables were allowed to enter the model separately.
관상동맥우회술 후 이식한 복재정맥의 재협착이나 폐쇄는 흔하며, 환자 및 수술적 요인과 관련이 있다

: PREVENT IV 연구로부터의 견해

나승운 교수 고려대학교 구로병원 순환기내과

Summary

배경
관상동맥우회술(coronary artery bypass grafting, CABG)의 성공은 복재정맥의 이식 실패(vein graft failure, VGF)에 의해 제한된다. VGF와 관련된 요인들을 이해하면 환자의 임상 결과를 항상시킬 수 있을 것이다.

방법 및 결과
PREVENT IV(Project of Ex Vivo Vein Graft Engineering via Transfection IV) 연구에 참여한 1,828명의 환자를 대상으로 분석을 진행하였다. 이 연구에서는 프로토콜상 의무적으로 CABG 12-18개월 이후 추적 혈관조영술을 시행하거나, 그 이전에 임상증상이 발생하게 되는 경우 추적 혈관조영술을 시행하게 되어 있었다. 임상 결과는 환자- 및 이식편- 수준의 VGF(≥75% 협착 또는 폐쇄)가 포함되었다. 변수는 빠른 거짓 선택 평가 방법론(Fast False Selection Rate methodology)을 사용하여 선택하였다. 연구자들은 일반화 추정 방정식을 포함 또는 제외하는 로지스틱 회귀 분석을 사용하여 환자- 및 이식편- 수준의 모델에서 변수들과 VGF 사이의 관계를 조사하였다. CABG 12-18개월 후 782/1,828명(42.8%)의 환자에서 VGF가 발생하였고, 1,096/4,343(25.2%)의 이식편에서 VGF가 발생하였다. 인구 통계학적 및 임상적 특성을 보존은 VGF가 발생한 환자를 그룹 착용한 환자에서 차이가 있었다. 다만, VGF 환자들은 외과적 수술 시간이 더 길었고, 목표 혈관의 상태가 좋지 않았던 경우가 많았으며, 이식 복재정맥의 길이가 더욱 긴 경우가 많았고, 내시경 정맥 수확을 한 경우가 많았다. 다변량 조정 후, 건 수술 시간(10분 증가 시마다 OR, 1.05; 95% CI, 1.03-1.07), 내 시경 정맥 수확(OR, 1.41; 95% CI, 1.16-1.71), 적절치 않은 목 표 혈관 상태(OR, 1.43; 95% CI, 1.11-1.84)와 clopidogrel 또는 ticlopidine의 수술 후 사용(OR, 1.35; 95% CI, 1.07-1.69)은 환 자-수준 VGF와 관련 있었다. 이식편-수준 VGF 모델의 예측 가능성을 12.1-63.6%였다.

결론
VGF는 CABG 후 흔히 발생하며, 환자 및 수술적 요인과 관련이 있다. 이러한 연구 결과는 VGF 위험인자를 가진 환자들을 식별하는 데 도움이 되고, VGF를 줄이기 위한 중재적 방법을 개발하는 데 중요한 정보를 제공해 줄 것으로 보인다.