Correlates of Saphenous Vein Graft Hyperplasia and Occlusion 1 Year After Coronary Artery Bypass Grafting: Analysis From the CASCADE Randomized Trial

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Background—Intimal hyperplasia of saphenous vein grafts (SVGs) can lead to subsequent graft atherosclerosis and occlusion after coronary artery bypass grafting (CABG). This study examined whether patient characteristics, anatomic factors, and medications are associated with SVG intimal hyperplasia and occlusion after CABG.

Methods and Results—We performed a post hoc analysis of the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial, where 322 grafts were assessed by angiography and 90 grafts were examined by intravascular ultrasound at 1 year after CABG. We assessed the following correlates for intimal hyperplasia and occlusion: patient characteristics, discharge medications, target vessel characteristics, and SVG diameter. At 1 year, the SVG mean intimal area was 4.3±2.1 mm², and the occlusion rate was 6.2% (13/209). Independent correlates of hyperplasia were larger SVG diameter (1.9±0.2 mm²; P<0.001), hypertension (0.7±0.3 mm²; P=0.03), and grafting to the right coronary territory (0.6±0.3 mm²; P=0.03), whereas statin (−0.8±0.3 mm²; P=0.01) and β-blocker use (−1.0±0.4 mm²; P=0.03) were associated with less hyperplasia. Low target vessel quality was an independent correlate of SVG occlusion (odds ratio, 5.2±3.1; P<0.01).

Conclusions—Hypertension, SVG diameter, grafting to the right coronary artery, and low quality of the target vessel correlate with the development of SVG hyperplasia or occlusion by 1 year after CABG, whereas β-blockers and statins are associated with less SVG disease. These new findings further our understanding of SVG remodeling after bypass surgery and may guide future research to help prevent post-CABG SVG disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00228423

Key Words: β-blockers, adrenergic • coronary artery bypass surgery • hyperplasia • saphenous vein

Saphenous vein grafts (SVGs) are widely used for coronary artery bypass grafting (CABG) because of their availability and ease of use. Previous studies have reported that aspirin and lipid-lowering agents are protective against SVG failure, and these are routinely administered in the postoperative period. Despite the use of these medications, the SVG failure rate remains high, and, in some series, ≤20% of SVGs occlude within the first year after CABG. Historically, by 10 years after surgery, only 60% of SVGs remain patent, and half of those that are patent have clinically important stenosis. Furthermore, target vessels for CABG have become increasingly diffusely diseased with atherosclerosis, calcification, and smaller diameter, because percutaneous coronary interventions have developed and expanded. Consequently, there is a need for other protective approaches against SVG failure to improve patency and clinical outcomes.

Intimal hyperplasia is one of the mechanisms of SVG failure, and its development and localization relate to that of subsequent atherosclerotic lesions. The Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) randomized controlled trial was designed to examine whether adding clopidogrel to aspirin was protective against SVG hyperplasia and occlusion, assessed by 1-year angiography supplemented with intravascular ultrasound (IVUS). The CASCADE trial previously reported that consistent statin use was significantly associated with a reduction in intimal hyperplasia of SVGs and that clopidogrel use was not.

Intimal hyperplasia in SVGs seems to be an adaptive response of the vein to arterial circulation, which stimulates proliferation and migration of vascular smooth muscle cells. Therefore, it is possible that the process of hyperplasia may be affected by hemodynamic parameters, medications, and anatomic factors. In this secondary analysis of the CASCADE...
trial, we evaluated hemodynamic, pharmacological, and anatomic factors as potential risk factors for SVG intimal hyperplasia and occlusion 1 year after CABG.

Methods
CASCADE was a dual-center, double-blind, placebo-controlled trial, which investigated the effect of clopidogrel on the development of SVG disease 1 year after CABG.12 The protocol was approved by each institutional research ethics board, and informed patient consent was acquired before each enrollment.

Population
This is a post hoc analysis of prospectively collected data from the CASCADE trial. Details of the study protocol have been previously published.12 At 2 centers, 113 patients who underwent CABG using ≥2 SVGs were enrolled in the trial. The degree of proximal stenosis in native target coronaries was assessed by preoperative angiography. At operation, the size of each target vessel was measured and its quality graded by the surgeon as good, fair, or poor according to the degree of local atherosclerosis. The greater saphenous vein was harvested using an open technique; endoscopic methods were not used in the CASCADE trial. Immediately after surgery, randomization was performed, and patients received either daily aspirin 162 mg plus clopidogrel 75 mg or aspirin 162 mg plus placebo starting on the day of surgery for a duration of 12 months.

Patient Follow-Up, Postoperative Angiography, and IVUS
Follow-up was performed with visits at 1, 6, and 12 months after operation and telephone home assessments at 3 and 9 months. All patients were treated in accordance with current American College of Cardiology/American Heart Association guidelines,16 which include aggressive diabetes mellitus management, smoking cessation counseling, and pharmacotherapy, including aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins as tolerated. Patients underwent angiography of the bypass grafts and the native coronary arteries 12 months after CABG, during which systolic blood pressure underwent angiography of the bypass grafts and the native coronary arteries 12 months after CABG. During angiography, the size of each target vessel was measured and its quality graded as A, B, or C by ≥2 independent blinded observers, according to the Fitzgibbon classification.17 During angiography, intimal hyperplasia of a randomly selected SVG was assessed by IVUS. A 40-MHz IVUS catheter (Atlantis SR Pro; Boston Scientific Corporation, Natick, MA) was inserted into a randomly selected SVG, and study images were recorded using a validated motorized pullback device at 0.5 mm/s. Subsequently, using digitized images in a core laboratory, manual planimetric measurements of cross sections spaced at 1.0-mm intervals were obtained, in accordance with established standards.18 The most proximal 40-mm segment of the SVG was analyzed. For each cross section analyzed, the lumen and external elastic lamina area were measured, and the area of intimal hyperplasia and SVG diameter were determined. Mean intimal area and mean SVG diameter per patient were calculated for the 40-mm analyzed segment.

Statistical Analysis
Data were analyzed in SPSS version 20.0 (IBM Corp, Armonk, NY) and Intercooled Stata 11.0 (Stata; College Station, TX). In this post hoc analysis of the CASCADE trial, we assessed whether patient characteristics, hemodynamics, medications, and anatomic factors are associated with SVG intimal hyperplasia and occlusion. Continuous data are presented as mean±SD. Univariable and multivariable stepwise linear regression analyses were performed to evaluate correlates of SVG intimal hyperplasia. The following factors were considered: age, sex, body mass index, diabetes mellitus, current smoking, a diagnosis of hypertension, hyperlipidemia, a history of acute coronary syndrome, preoperative creatinine, 1-year follow-up hemodynamics (systolic BP, diastolic BP, and resting heart rate), medication profile (before surgery, at discharge, and at 3, 6, and 12 months of follow-up, including aspirin, clopidogrel, β-blockers, statins, calcium channel blockers and angiotensin-converting enzymes), consistent use of statins throughout the trial period, % stenosis of native target coronary artery, target vessel location (right coronary artery [RCA] or left coronary artery), target vessel quality (good or fair/poor), target vessel size, and SVG diameter (as assessed by IVUS). Only variables that had a P<0.20 in univariable analysis were considered in the multivariable linear regression model using stepwise forward selection and backward elimination techniques (P<0.20 for entry and 0.20 for removal criteria). In addition, diabetes mellitus, the consistent use of statins, hypertension, and the use of calcium channel blockers at discharge were forced into the final model, because they had been noted to be significant correlates of SVG intimal hyperplasia in previous studies. In the adjusted model for intimal hyperplasia area, statistically significant variables are each noted with a regression coefficient±SE.

To evaluate the correlates of SVG occlusion, we assessed, on univariable analysis, the same variables as in the analysis of correlates of SVG intimal hyperplasia, except for SVG diameter (not available from occluded grafts). To account for within-patient correlation and the possibility of multigraft occlusion within individual patients, as well as to avoid model overfitting, vein graft occlusion data were modeled using generalized estimating equations, incorporating only correlates that were statistically significant on univariable analysis. All reported P values are 2-sided, and statistical significance was set at p<0.05.

Results
In the CASCADE trial, 113 patients were enrolled between May 2006 and July 2009 at the University of Ottawa Heart Institute (Ottawa, Ontario, Canada) and Hôpital Laval (Quebec City, Quebec, Canada). Twelve-month angiography was completed for 322 grafts in 92 of the 113 enrolled patients (81.4%). Table 1 shows the preoperative characteristics of 92 patients.

Discharge medications in these 92 patients were β-blockers in 90.2%, lipid-lowering medications in 89.1%, calcium channel blockers in 10.9%, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 33.7%. At 12-month follow-up, 82.6% of patients were using β-blockers, 95.7% lipid-lowering drugs, 16.3% calcium channel blockers, and 42.4% were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Mean follow-up duration was 13.1±4.5 months. At 1 year, mean systolic BP and mean diastolic BP were 135±26 and 65±11 mm Hg, respectively, and mean resting heart rate was 63±12 bpm. Overall 1-year patency was 307 of 322 examined grafts (95.3%). One-year internal thoracic artery graft patency was 98.2% (110/112), and 1-year SVG patency was 93.8% (196/209). The rate of vein graft stenosis was 2.9% (6/209). Table 2 shows the anatomic characteristics of the 209 SVGs examined.

Ninety of the 92 patients assessed by angiography also underwent IVUS. IVUS could not be performed in 2 patients because of technical factors (1 patient) or the presence of 2 occluded SVGs (1 patient). The anatomic characteristics of the 90 SVGs assessed by IVUS are shown in Table 2.

Correlates of Intimal Hyperplasia
Mean intimal area of the randomly selected 90 SVGs was 4.31±2.06 cm². On univariable analysis, SVGs with a larger diameter (2.09±0.18 mm² per mm increase; P<0.001), the use of β-blockers at discharge (by −1.48±0.71 mm²; P=0.04), and SVGs grafted to the RCA (by 1.03±0.43 mm²;
P=0.02) correlated with the degree of intimal hyperplasia. On multivariable stepwise linear regression analysis, significant independent correlates of intimal hyperplasia were SVG diameter (1.91±0.18 mm² per mm increase; P<0.001), hypertension (by 0.70±0.32 mm²; P=0.03), and grafting to the RCA (by 0.61±0.28 mm²; P=0.03), as shown in Table 3. Factors that were significantly associated with less intimal hyperplasia included consistent use of statins (by −0.79±0.31 mm²; P=0.01) and β-blocker use at discharge (by −1.02±0.44 mm²; P=0.03). Medications at 3-, 6-, or 12-month follow-up were not significantly associated with SVG intimal hyperplasia. Hemodynamic parameters at 1-year follow-up were also not significantly associated with intimal hyperplasia.

Correlates of SVG Occlusion
On univariable analysis, significant correlates of SVG occlusion included female sex (odds ratio, 4.1±2.6; P=0.03) and low (ie, fair or poor) target vessel quality (odds ratio, 5.8±3.5; P<0.01). On multivariable analysis, fair/poor target vessel quality was a significant correlate (odds ratio, 5.2±3.1; P<0.01), and female sex showed a strong trend (odds ratio, 3.5±2.3; P=0.055; Table 4).

Clinical Outcomes
Twelve-month follow-up was completed for all the 92 patients, of whom 5 patients (5.4%) had nonfatal myocardial infarction and 3 patients (3.3%) required percutaneous coronary interventions after CABG. One patient who presented 10 months postoperatively with a non–ST-elevation myocardial infarction was noted to have 2 occluded vein grafts at angiography; stenting of 1 vein graft and the native left main coronary artery was performed. Another patient presented 7 months postoperatively with a non–ST-elevation myocardial infarction; all grafts were patent at angiography, and percutaneous coronary interventions were performed for a new circumflex artery lesion. The third patient presented 11 months postoperatively with chest pain; at angiography, all grafts were patent, and stenting of a new RCA lesion was performed.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.0±7.4</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.5±3.9</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (29.3)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>72 (78.3)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>83 (90.2)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>Myocardial infarction &lt;6 wk, n (%)</td>
<td>17 (18.5)</td>
</tr>
<tr>
<td>Angina CCS classes 3–4, n (%)</td>
<td>52 (56.5)</td>
</tr>
<tr>
<td>Heart failure NYHA classes 3–4, n (%)</td>
<td>21 (22.8)</td>
</tr>
<tr>
<td>Preoperative creatinine, μmol/L</td>
<td>87.8±17.5</td>
</tr>
</tbody>
</table>

Table 1. Patient Characteristics

Preoperative medication use
- Aspirin, n (%) 85 (92.4)
- Clopidogrel, n (%) 9 (9.8)
- Statins, n (%) 81 (88.0)
- β-Blockers, n (%) 71 (77.2)
- Angiotensin-converting enzyme inhibitors, n (%) 46 (50.0)
- Calcium channel blockers, n (%) 13 (14.1)

Operative details
- No. of distal anastomoses, n 3.5±0.7
- Left internal thoracic graft, n (%) 92 (100.0)
- Right internal thoracic graft, n (%) 21 (22.8)
- Cross-clamp time, min 65.1±21.2
- Cardiopulmonary bypass time, min 89.1±25.8
- Off-pump surgery, n (%) 4 (4.3)

Postoperative length of stay
- Duration in intensive care, d 1.4±1.0
- Duration in hospital, d 8.5±5.8

Medications at discharge
- Aspirin, n (%) 92 (100.0)
- Clopidogrel, n (%) 46 (50.0)
- Statins, n (%) 82 (89.1)
- β-Blockers, n (%) 83 (90.2)
- Angiotensin-converting enzyme inhibitors, n (%) 31 (33.7)
- Calcium channel blockers, n (%) 10 (10.9)
- Consistent use of statins during first year, n (%) 66 (71.7)

Table 2. Anatomic Factors of 209 SVGs Assessed by Angiography and 90 SVGs Assessed by IVUS

<table>
<thead>
<tr>
<th>Variables</th>
<th>SVGs Assessed by Angiography (n=209)</th>
<th>SVGs Assessed by IVUS (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel location</td>
<td>RCA 78/209 (37%)</td>
<td>36/90 (40%)</td>
</tr>
<tr>
<td></td>
<td>Circumflex 100/209 (48%)</td>
<td>46/90 (51%)</td>
</tr>
<tr>
<td></td>
<td>Diagonal branch 31/209 (15%)</td>
<td>8/90 (9%)</td>
</tr>
<tr>
<td>Target vessel size</td>
<td>1.0–1.4 mm 22/209 (11%)</td>
<td>9/90 (10%)</td>
</tr>
<tr>
<td></td>
<td>1.5–2.0 mm 140/209 (67%)</td>
<td>59/90 (66%)</td>
</tr>
<tr>
<td></td>
<td>≥2.1 mm 47/209 (22%)</td>
<td>22/90 (24%)</td>
</tr>
<tr>
<td>Target vessel quality</td>
<td>Good 143/209 (69%)</td>
<td>63/90 (70%)</td>
</tr>
<tr>
<td></td>
<td>Fair 57/209 (27%)</td>
<td>23/90 (26%)</td>
</tr>
<tr>
<td></td>
<td>Poor 9/209 (4%)</td>
<td>4/90 (4%)</td>
</tr>
<tr>
<td>Proximal stenosis of native target vessel</td>
<td>50–99% 118/209 (57%)</td>
<td>47/90 (52%)</td>
</tr>
<tr>
<td></td>
<td>90–99% 51/209 (24%)</td>
<td>22/90 (25%)</td>
</tr>
<tr>
<td></td>
<td>100% 40/209 (19%)</td>
<td>21/90 (23%)</td>
</tr>
<tr>
<td>SVG diameter, mm</td>
<td>4.0±0.8</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Intimal hyperplasia in SVGs is linked to subsequent graft atherosclerosis and failure. Identifying its magnitude, causes, and correlates may provide surrogate information to steer further research and help improve SVG patency and clinical outcomes after CABG. This secondary analysis of CASCADE is the first study to focus on intimal hyperplasia in the context of a prospective clinical trial. To this end, we used quantitative IVUS assessment after CABG and identified correlates for the development of intimal hyperplasia and SVG occlusion, by assessing patient characteristics, hemodynamic parameters, relevant medications, and anatomic factors. In addition to the use of statins, we found that β-blocker use, graft size, graft location, and hypertension were significantly associated with SVG intimal hyperplasia and that female sex and low target quality correlated with graft occlusion at 1 year postoperatively.

β-Blockers and SVG Remodeling

The use of β-blockers at discharge was significantly associated with less intimal hyperplasia. One possible mechanism by which β-blockers may inhibit SVG remodeling is by reducing the temporal gradient of blood flow, which affects graft blood flow velocity. White et al previously reported that more steady blood flow leads to less SVG remodeling. In this regard, temporal gradients of shear stress are inversely proportional to the cube of vessel radius, suggesting that larger grafts have less shear stress and, as a result, more hyperplasia. In addition to this relationship, small conduits are less likely to have graft-target vessel size mismatch, which may cause hyperplasia and thrombosis as a result of flow turbulence.

Only the use of β-blockers at discharge was a correlate, rather than at 3, 6, or 12 months. Tran-Son-Tay et al previously showed that SVG walls are particularly susceptible to remodeling early after CABG and that hyperplasia growth becomes slower over time. Based on the above and the findings of the current study, the use of β-blockers early after CABG may be particularly important in keeping with current clinical guidelines, supporting their use to prevent adverse events in the postoperative period.

Recently, animal studies have reported that third-generation β-blockers (nebivolol and celiprolol) inhibit the formation of intimal hyperplasia and dilate coronary microarteries through enhanced nitric oxide production. In the CASCADE trial, 81 of the 90 patients (90.0%) who underwent angiography were on β-blockers at discharge. Of the 81 patients, 72.8% were on metoprolol, 19.8% on bisoprolol, 3.7% on atenolol, and 3.7% on acebutolol. There were no patients on third-generation β-blockers, implying that a decrease in dp/dr alone may have been responsible for reducing intimal hyperplasia. It is possible that nebivolol and celiprolol may be more effective in reducing post-CABG intimal hyperplasia in humans, with the addition of their nitric oxide-based mechanism, highlighting an area for future research.

Graft Size and SVG Remodeling

A larger SVG diameter was associated with more intimal hyperplasia. This is consistent with a previous study which reported that larger diameter SVGs are a risk factor for SVG failure. Intimal thickening is inversely related to shear stress, and in a mathematical model of steady laminar flow, shear stress is inversely proportional to the cube of vessel radius, suggesting that larger grafts have less shear stress and, as a result, more hyperplasia. In addition to this relationship, small conduits are less likely to have graft-target vessel size mismatch, which may cause hyperplasia and thrombosis as a result of flow turbulence.

The best harvest site of SVGs remains unclear. The SVG diameter–patency relationship elicited in this study implies that distal veins may have better patency than proximal veins, which is consistent with a previous study. However, in the CASCADE trial, SVGs were harvested almost exclusively from the thigh, in an open fashion, and the 1-year angiographic patency rate of SVGs was high at 93.8%, encouraging one to continue using upper leg veins.

Target Vessel Location and SVG Remodeling

Grafting of the RCA territory was a significant risk factor for SVG remodeling. In this regard, temporal gradients of shear stresses have been reported to induce more intimal hyperplasia than steady shear stresses. The bimodal flow pattern (systolic and diastolic) of grafts to the RCA may stimulate SVG walls and lead to a higher degree of hyperplasia than the monomodal flow pattern usually observed in grafts to the left coronary system. Previous studies have also shown that patency is generally lower for SVGs grafted to the right coronary system compared with those grafted to the left.

Table 3. Independent Correlates of SVG Intimal Hyperplasia

<table>
<thead>
<tr>
<th>Variables in the Final Model</th>
<th>Coefficients</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Significant correlates</td>
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<tr>
<td>SVG diameter</td>
<td>1.91±0.18 mm² per mm increase</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>By 0.70±0.32 mm²</td>
<td>0.03</td>
</tr>
<tr>
<td>Grafting of the RCA</td>
<td>By 0.61±0.28 mm²</td>
<td>0.03</td>
</tr>
<tr>
<td>Consistent use of statins</td>
<td>By −0.79±0.31 mm²</td>
<td>0.01</td>
</tr>
<tr>
<td>β-Blocker use at discharge</td>
<td>By −1.02±0.44 mm²</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-significant correlates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>By −0.58±0.30 mm²</td>
<td>0.059</td>
</tr>
<tr>
<td>Calcium channel blockers at discharge</td>
<td>By −0.74±0.45 mm²</td>
<td>0.10</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; and SVG, saphenous vein graft.

Table 4. Independent Correlates of SVG Occlusion

<table>
<thead>
<tr>
<th>Variables in the Final Model</th>
<th>Odds Ratio</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Significant correlates</td>
<td></td>
<td></td>
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<tr>
<td>Target vessel quality (fair/poor)</td>
<td>5.2±3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-significant correlates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.5±2.3</td>
<td>0.055</td>
</tr>
</tbody>
</table>

SVG indicates saphenous vein graft.
Hypertension and SVG Remodeling
This study showed that a diagnosis of hypertension was a risk factor for SVG intimal hyperplasia. Hypertension is a well-known risk factor for medial hyperplasia. Alternatively, BP at 1-year follow-up was not a risk factor. This may reflect that continuous arterial pressure loads, particularly early after surgery, are more important than BP measurements at isolated time points after CABG. This may reflect a particular need to control BP during the early postoperative period because intimal hyperplasia can develop as early as 4 to 6 weeks after surgery.1,18

Statins and SVG Remodeling
Consistent statin use throughout the trial period was associated with less SVG intimal hyperplasia. We previously reported that 12-month graft patency was significantly lower for patients who had low-density lipoprotein levels >100 mg/dL compared with those who had low-density lipoprotein levels <100 mg/dL; whereas further reduction to <70 mg/dL was not associated with additional improvement in another secondary analysis of the CASCADE trial. Although the use of statins was advocated for all enrolled patients in the CASCADE trial, 10.9% of patients were not on statins at discharge because of allergy or nausea. However, compliance increased to 95.7% by 12 months after surgery.

Sex and SVG Patency
In this study, univariable analysis showed that female patients were more likely to develop SVG occlusion. Although only a strong trend was observed on multivariable analysis, this observation is consistent with a previous study which reported that SVG patency in women was inferior to that in men. This may reflect smaller coronary artery size in women.28

Target Vessel Quality and SVG Patency
Target vessel quality was an independent correlate of SVG occlusion. Although many articles have reported that the size of a target coronary vessel is an independent risk factor for SVG occlusion, few have noted that a poor angiographic distal bed quality is a risk factor for SVG occlusion at 1 year after CABG.29 In the present study, the quality of target vessel was graded with intraoperative assessment of the anastomotic site. Although this was a subjective gradation, intuitively, thrombus is more likely to develop in a calcified and atherosclerotic vessel early after CABG compared with a relatively healthy distal target vessel.

Limitations
With so few studies having focused on intimal hyperplasia in humans, there is no demonstrated clinical relationship between SVG hyperplasia and long-term SVG patency or late outcomes of CABG patients.1

Limitations of this study include those inherent to smaller studies. Graft flow was not measured. Compared with other studies, graft patency was high, which could affect generalizability. Major adverse cardiac events were too few to statistically evaluate their relationship with intimal hyperplasia or graft occlusion. IVUS assessment was limited only to the proximal 40-mm segment of SVGs to avoid a wire across the anastomosis, thereby minimizing the risk of trauma to the anastomosis or native coronary artery; in this regard, we assumed that the proximal 40-mm segment would provide a proportional indicator of the degree of intimal hyperplasia in each graft, with randomly distributed variability. Finally, SVG diameter was calculated from IVUS results and not from intraoperative assessments.

Conclusions
Within the CASCADE trial CABG population, in addition to the consistent use of statins, the use of β-blockers at discharge was associated with less SVG intimal hyperplasia, whereas a larger diameter of SVGs, hypertension, and grafting of the RCA territory were risk factors for its increased magnitude. Furthermore, low target vessel quality and female sex were risk factors for SVG occlusion. These findings provide novel data on intimal hyperplasia and its determinants and may guide subsequent research toward improving SVG patency and clinical outcomes after CABG.

Sources of Funding
The CASCADE trial was funded by research grants from the Physicians’ Services Incorporated Foundation, from Boston Scientific Inc, and from the Bristol-Myers Squibb Sanofi Canada Partnership. Boston Scientific supplied the intravascular ultrasound catheters used during the course of this study. The Bristol-Myers Squibb Sanofi Canada Partnership provided the study medication (clopidogrel and matching placebo) and financial support for the trial. The study authors alone designed this sub-study of the trial, analyzed and interpreted the data, wrote the article, and decided to submit the article for publication. The authors attest to the completeness and accuracy of data gathering and analysis.

Disclosures
Drs Ruel and Le May received research support from the Bristol-Myers Squibb Sanofi Canada Partnership for the conduct of the CASCADE trial. The other authors report no conflicts.

References


