Do Differences in Repeat Revascularization Explain the Antianginal Benefits of Bypass Surgery Versus Percutaneous Coronary Intervention?

Implications for Future Treatment Comparisons

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Background—Patients with multivessel coronary disease treated with coronary artery bypass graft (CABG) have less angina than those treated with percutaneous coronary intervention (PCI); however, there is uncertainty as to the mechanism of greater angina relief with CABG and whether more frequent repeat revascularization in patients treated with PCI could account for this treatment difference.

Methods and Results—In the Synergy between percutaneous coronary intervention (PCI) with TAXUS and Cardiac Surgery trial, 1800 patients with 3-vessel or left main coronary artery disease were randomized to CABG or PCI with paclitaxel-eluting stents. Health status was assessed at baseline, 1, 6, and 12 months, using the Seattle Angina Questionnaire and the Medical Outcomes Study Short Form General Health Survey, and the association between repeat revascularization and health status during follow-up was assessed using longitudinal models. In adjusted analyses, patients who underwent repeat revascularization had worse angina frequency scores than patients who did not in both treatment groups, with differences of 8.5 points at 6 months and 3.1 points at 12 months in patients treated with PCI and 19.8 points at 6 months and 11.2 points at 12 months in patients treated with CABG. Among patients who did not require repeat revascularization, the adjusted effect of CABG versus PCI on 12-month angina frequency scores was nearly identical to the overall benefit in the intention-to-treat analysis.

Conclusions—Among patients with multivessel coronary artery disease treated with PCI or CABG, the occurrence of repeat revascularization during follow-up did not fully explain the antianginal benefit of CABG in the overall population. The differential association between repeat revascularization and anginal status, according to the type of initial revascularization procedure, suggests that this end point should play a limited role in any direct comparison of the 2 treatment strategies.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00114972.

Key Words: percutaneous coronary intervention ■ coronary artery bypass grafting ■ angina ■ drug-eluting stents ■ quality of life

In patients with left main or multivessel coronary artery disease, the Synergy between percutaneous coronary intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) trial found that the rate of the composite primary end point (death, myocardial infarction, stroke, or repeat revascularization) was lower at 12 months with coronary artery bypass grafting (CABG) than with PCI using paclitaxel-eluting stents; however, the overall result was driven largely by a reduction in repeat revascularization, and the combined end point of irreversible outcomes (death, myocardial infarction, or stroke) did not differ significantly between the 2 strategies.

In the SYNTAX quality-of-life substudy, patients randomized to CABG had a small but significant improvement in angina at 6 and 12 months as compared with those randomized to PCI.2 Previous studies have suggested that differences in angina relief and quality of life between PCI and CABG may be largely explained by differences in rates of residual or recurrent ischemia between these 2 revascularization strategies, driven largely by the higher rate of restenosis after balloon angioplasty or stent placement.3,4 According to this
paradigm, ongoing and future advances in PCI technique and technology that lead to reductions in rates of repeat revascularization might allow patients treated with PCI to achieve quality-of-life benefits comparable to those seen with CABG, even in patients with complex coronary artery disease. To examine this concept in greater detail, we used data from the SYNTAX trial to explore the association between repeat revascularization procedures and follow-up health status among patients with multivessel or left main coronary artery disease treated with either CABG or PCI.

WHAT IS KNOWN

• The SYNTAX trial found that patients with left main or multivessel coronary disease treated with initial CABG surgery had lower rates of repeat revascularization and less angina than those treated with initial PCI.

WHAT THE STUDY ADDS

• Using the SYNTAX population, we evaluated the relationship between initial treatment, repeat revascularization during follow-up, and angina at 1 year. We found that patients who underwent repeat revascularization had worse angina frequency scores than patients who did not in both treatment groups, similar to other studies.
• Among patients who did not undergo repeat revascularization, patients treated with CABG still had better angina relief at 12 months than patients treated with PCI, with an adjusted between-group difference similar to the treatment effect in the overall population. These findings suggest that some of the antianginal benefits of CABG may result from mechanisms unrelated to relief of myocardial ischemia (eg, denervation, placebo effects).
• The strength of association between repeat revascularization and angina was greater among patients treated with CABG as compared with those treated with PCI, indicating that the end point of repeat revascularization has a different clinical impact based on the original treatment and thus should play a limited role as an indirect measure of health outcomes between these 2 revascularization strategies.

Outcome Measurements and Definitions

Health status was assessed with standardized, written questionnaires at baseline and at 1, 6, and 12 months after randomization. Patients completed baseline questionnaires before randomization and subsequent questionnaires at the time of scheduled follow-up visits or by mail. Questionnaires were administered in each patient’s native language. Of the 18 countries that participated in the SYNTAX trial, validated translations were available for 15 countries for the Seattle Angina Questionnaire (SAQ) and for all countries for the Medical Outcomes Study Short Form General Health Survey (SF-36). Follow-up rates for quality-of-life responses were >90% for surviving patients at all time points (baseline: 96.2%; 1 month: 90.5%; 6 months: 90.3%; 12 months: 90.5%).

Disease-specific health status was assessed using the SAQ: a validated 19-item questionnaire that measures 5 domains of health status related to coronary artery disease: angina frequency, physical limitations, quality of life, angina stability, and treatment satisfaction. The angina stability domain was not included in this study because it is a cross-sectional measure of short-term change in health status, which presents challenges in interpretation for longitudinal analysis. Scores for each of the domains range from 0 to 100, with higher scores indicating less disease burden. The minimum clinically important difference is 8 to 10 points for the SAQ angina frequency, physical limitations, and quality-of-life subscales and 5 points for the treatment satisfaction scale.

Generic health status was evaluated using the SF-36, which assesses 8 dimensions of health: physical functioning, role limitations due to physical problems, bodily pain, vitality, general health perception, social function, role limitations due to emotional problems, and mental health. The SF-36 also provides summary scales for overall physical and mental health that were created using norm-based methods that standardize the scores to a mean of 50 and a standard deviation of 10. Scores for each domain of the SF-36 range from 0 to 100, with higher scores indicating better health status. The minimum clinically important difference is 5 to 10 points for the individual subscales of the SF-36 and 2.5 to 5 points for the physical and mental summary scales.

For the purposes of this analysis, repeat revascularization was defined as any repeat PCI or CABG procedure between initial hospital discharge and 12 months of follow-up (excluding staged PCI that was planned and completed within 14 days of the index PCI). Of note, protocol-driven angiography was not performed in SYNTAX, and thus all follow-up interventions were performed according to the clinical judgment of the treating physician. Complete revascularization during the index procedure was defined as the successful treatment of all eligible lesions identified during the local Heart Team conference at the time of study enrollment.

Statistical Analysis

As previously described, the prespecified primary end point of the quality-of-life analysis was the SAQ angina frequency scale. Baseline characteristics were compared between patients with and without repeat revascularization procedures using the χ² test for categorical variables and Student t test for continuous variables. Baseline health status scores were compared between groups using analysis of variance, and follow-up health status scores were compared using analysis of covariance, adjusting for baseline scores.

To explore the association between repeat revascularization and follow-up health status, we developed longitudinal, random-effect mixed-effects models to examine the extent to which this factor might account for observed treatment differences. In these analyses, repeat revascularization was not considered as a time-dependent covariate, since our goal was to understand the extent to which patients undergoing repeat revascularization accounted for the previously described health status differences between CABG and PCI. Variables in the models for each outcome included treatment assignment, age, diabetes, baseline angina (defined as present [SAQ angina frequency score <100] or absent [SAQ angina frequency score=100]), presence of significant left main disease, SYNTAX score (an anatomic assessment of coronary artery severity, based on the diagnostic angiogram, with higher scores indicating more...
complex disease; analyzed as tertiles: 0 to 22, 23 to 32, and 33 to 83), completeness of revascularization, repeat revascularization (at any point >12 months of follow-up), follow-up time, the interaction between treatment group and repeat revascularization, the interaction between treatment group and time, and the 3-way interaction among treatment group, time, and repeat revascularization. The intercept and linear time effects were estimated using both fixed and random effects, while quadratic and cubic effects of time were modeled as fixed effects, to avoid overparameterization. For each variable in the model, a mean effect was estimated, along with a 95% confidence interval (CI).

To aid with interpretation, we calculated an effect size for the association between repeat revascularization and each health status domain by dividing the mean difference in the score between those who did and did not require repeat revascularization by the pooled standard deviation. For these calculations, the accepted thresholds for small-, moderate-, and large-effect sizes are 0.20, 0.50, and 0.80, respectively. 10

All tests of statistical significance were 2-tailed, and \( P < 0.05 \) was considered statistically significant. All statistical analyses were performed using SAS for Windows version 9.2 (SAS Institute, Inc). The authors had full access to and take full responsibility for the integrity of the data.

Results

Patient Population and Clinical Outcomes

Between hospital discharge and 12-month follow-up, 6.1% of patients randomized to CABG (n = 897) underwent diagnostic catheterization, and 4.0% required repeat revascularization. During the same time period, 19.1% of patients randomized to PCI (n = 903) underwent diagnostic catheterization, and 11.5% required revascularization. More than 80% of all repeat revascularization procedures were PCI (91/104 among patients treated initially with PCI and 35/36 among patients who initially underwent CABG). Approximately half of the repeat revascularization procedures in both treatment groups occurred in the first 6 months after the index procedure (19/36 [53%] of patients treated with CABG and 51/104 [49%] of patients treated with PCI), with the remainder occurring between 6 and 12 months of follow-up. Baseline characteristics of patients who did and who did not require revascularization over the follow-up period are summarized in Table 1. Patients who required repeat revascularization were more likely to be non-white and have diabetes compared with those who did not; otherwise there were no statistically significant differences between the groups of patients.

Health Status Outcomes

Raw baseline and follow-up health status scores of patients who did and who did not require revascularization procedures are shown in Table 2. In general, health status scores were similar at baseline between groups, except for lower angina frequency scores (ie, more frequent angina) at baseline among those who required revascularization during follow-up (64.7 versus 70.0, \( P = 0.03 \)). In contrast, follow-up health status scores were nearly uniformly worse among those patients who underwent repeat revascularization compared with those who did not. Although differences were seen across all health status domains, the differences were most striking for the SAQ angina frequency and quality-of-life domains, where there were \( >10 \)-point differences between groups at the 6-month follow-up and 6- to 7-point differences at the 12-month follow-up.

Longitudinal Analyses

Results from the longitudinal growth curve models, which included baseline patient characteristics and procedural factors, demonstrated that older age, male sex, and absence of angina at baseline were associated with less angina at 12 months (Table 3). After adjusting for these factors, patients who required repeat revascularization had lower 6-month SAQ angina frequency scores (ie, worse angina) compared with patients who did not undergo repeat revascularization, with mean differences of 8.5 points (effect size 0.49) in the
PCI group and 19.8 points (effect size 1.37) in the CABG group (both P<0.001). These effects were somewhat attenuated at 12 months, with associated reductions of 3.1 points (effect size 0.20) in the PCI group (P=0.06) and 11.2 points (effect size 0.79) in the CABG group (P<0.001). Among patients who did not require repeat revascularization, the adjusted effect of CABG versus PCI on the SAQ angina frequency scale was 1.5 points at 6 months and 1.6 points at 12 months (higher for CABG). Of note, this effect was similar to the overall effect of CABG versus PCI in the intention-to-treat analysis of 1.8 points at 6 months and 1.6 points at 12 months, \(^2\) although it was no longer statistically significant in these analyses (P=0.07 at 6 months; P=0.06 at 12 months).

Results were generally similar for the other health status domains as well (Tables 4 and 5, Figure 1 and 2). At 6 months, the adjusted reduction in disease-specific health status scores among patients treated with PCI who underwent repeat revascularization during follow-up was 6.2 points (effect size 0.31) for the SAQ physical limitations domain and 11.4 points (effect size 0.49) for the SAQ quality-of-life domain. These effects were even larger among patients who underwent initial CABG, with adjusted reductions of 10.0 points (effect size 0.46) for the physical limitations domain and 15.3 points (effect size 0.71 points) for the quality-of-life domain. In terms of generic health status, mental health was worse among patients treated with CABG who required repeat revascularization compared with patients who did not, whereas physical health was impacted to a greater extent among patients treated with PCI. For virtually all domains, decrements in health status among patients with versus
without repeat revascularization were larger for patients treated with initial CABG as opposed to PCI.

At 12 months, patients treated with CABG who required repeat revascularization during follow-up continued to demonstrate worse disease-specific and generic health status compared with patients treated with CABG without repeat revascularization (Table 5; Figure 2). In contrast, patients treated with PCI who required repeat revascularization during follow-up had 12-month disease-specific and generic health status that was similar to those who did not.

**Discussion**

Among patients with 3-vessel or left main coronary artery disease, the SYNTAX trial found that the extent of improvement in SAQ angina frequency scores was slightly greater with CABG than with PCI with paclitaxel-eluting stents, with a mean adjusted between-group difference of 1.8 points at 6 months and 1.6 points at 12 months. The current study provides additional important insights as to the mechanism of those observed treatment differences.

There are 2 main points to be understood from these analyses. First, as in previous studies, patients who required repeat revascularization during follow-up had more frequent angina, particularly at the 6-month assessment. This finding is not particularly surprising, since it is likely that, in many cases, recurrent (or persistent) angina actually prompted repeat coronary angiography and revascularization; however, even among patients who did not undergo repeat revascularization, patients treated with CABG still had better angina relief at 12 months, with a mean adjusted between-group difference of 1.6 points. Although this difference was no longer statistically significant in the adjusted analyses, the magnitude of difference was nearly identical to the main treatment effect. Thus, although patients treated with initial PCI experienced a substantially higher rate of repeat revascularization during the first year of follow-up, and patients who required repeat revascularization had worse angina and quality of life, differences in the need for repeat revascularization did not completely explain the treatment benefit of CABG over PCI in the overall population.

The second important finding of our study was the differential association between the need for repeat revascularization and follow-up angina frequency for patients treated with CABG versus PCI. Among patients randomized to PCI, the need for repeat revascularization was associated with reductions in SAQ angina frequency scores of 8.5 points at 6 months and 3.1 points at 12 months. In contrast, among patients randomized to CABG, these effects were 19.8 points at 6 months and 11.2 points at 12 months: more than twice as large as those observed after PCI. This variation may indicate a different threshold for physicians to consider reintervention or, perhaps, by patients to seek medical evaluation after CABG versus PCI. Regardless of the underlying explanation, however, this finding could have critical implications for comparisons of PCI versus CABG with respect to endpoints that incorporate repeat revascularization.

**Comparison to Prior Studies**

Prior studies have reported that the main clinical benefit of CABG over PCI is a reduction in the need for repeat revascularization, and the increased need for reintervention in the PCI group has been hypothesized to be a key mediator of the observed differences in angina status between the 2 treatment groups. As these studies were performed primarily in the era of balloon angioplasty or bare metal stents, one of the central hypotheses of the SYNTAX trial was that using a stent that substantially reduced restenosis and, thereby, the need for repeat procedures could narrow the treatment gap between PCI and CABG for multivessel coronary disease. Although the antianginal benefit of CABG over PCI was, indeed, attenuated in SYNTAX as compared with prior studies, our findings suggest that this difference cannot be attributed solely to differences in the rates of repeat revascularization.

Several previous studies have examined the association between repeat revascularization and the differential health status benefits of CABG versus PCI. In the Stent or Surgery

**Table 3. Estimated Impact of Patient Characteristics and Revascularization Outcomes on SAQ Angina Frequency Score**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Mean Effect</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>0.8</td>
<td>0.2 to 1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.8</td>
<td>1.3 to 4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.1</td>
<td>-1.5 to 1.2</td>
<td>0.85</td>
</tr>
<tr>
<td>SYNTAX Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.6</td>
<td>-0.8 to 2.1</td>
<td>0.40</td>
</tr>
<tr>
<td>High</td>
<td>0.4</td>
<td>-1.1 to 1.9</td>
<td>0.77</td>
</tr>
<tr>
<td>Left main disease</td>
<td>-0.04</td>
<td>-1.3 to 1.2</td>
<td>0.94</td>
</tr>
<tr>
<td>Angina at baseline</td>
<td>-0.99</td>
<td>-11.4 to -8.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete revascularization</td>
<td>-0.9</td>
<td>-2.1 to 0.4</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Effects at 6 mo

- CABG (no revasc) vs PCI (no revasc): 1.5, 0.2 to 3.2, 0.07
- CABG (with revasc) vs PCI (with revasc): -0.5, -16.0 to -3.5, 0.02
- Repeat revascularization (after PCI): -0.85, -11.9 to -5.1, <0.0001
- Repeat revascularization (after CABG): -19.8, -25.2 to -14.3, <0.0001

Effects at 12 mo

- CABG (no revasc) vs PCI (no revasc): 1.6, -0.04 to 3.2, 0.06
- CABG (with revasc) vs PCI (with revasc): -0.65, -12.8 to -0.3, 0.04
- Repeat revascularization (after PCI): -0.31, -6.3 to 0.1, 0.06
- Repeat revascularization (after CABG): -11.12, -16.8 to -5.6, <0.0001

SAQ indicates Seattle Angina Questionnaire; CI, confidence interval; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; revasc, revascularization.

*Results derived from longitudinal, random effects growth curve models (see methods for details).
trial, 988 patients with multivessel coronary artery disease were randomized to either CABG or PCI with bare metal stents. At 12 months, patients treated with CABG had improved SAQ angina frequency scores as compared with those treated with PCI, with a mean difference of 2.9 points. Patients treated with PCI who required repeat revascularization had worse angina and health status than those who did not, and this was hypothesized to be the main driver of the difference in the overall population; however, among patients who did not undergo repeat revascularization, there remained a mean treatment difference of 2.4 points in SAQ angina frequency scores between the patients treated with CABG and

### Table 4. Association Between Repeat Revascularization and Health Status at 6 Months, Based on Longitudinal, Random Effects Growth Curve Models

<table>
<thead>
<tr>
<th>Health Status Measure</th>
<th>CABG Group</th>
<th>PCI Group</th>
<th>Effect Size*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Effect</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td><strong>Seattle Angina Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina frequency</td>
<td>$-19.8^f$</td>
<td>$-25.2$ to $-14.3$</td>
<td>1.37</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>$-10.0^f$</td>
<td>$-17.2$ to $-2.8$</td>
<td>0.46</td>
</tr>
<tr>
<td>Quality of life</td>
<td>$-15.3^f$</td>
<td>$-22.6$ to $-8.0$</td>
<td>0.71</td>
</tr>
<tr>
<td>Treatment satisfaction</td>
<td>$-3.3$</td>
<td>$-8.2$ to $1.6$</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>36-item Short Form General Health Survey</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>$-6.7$</td>
<td>$-14.6$ to $1.1$</td>
<td>0.29</td>
</tr>
<tr>
<td>Role physical</td>
<td>$-4.3$</td>
<td>$-13.5$ to $5.0$</td>
<td>0.16</td>
</tr>
<tr>
<td>Role emotional</td>
<td>$-8.9$</td>
<td>$-17.8$ to $0.0$</td>
<td>0.34</td>
</tr>
<tr>
<td>Social function</td>
<td>$-8.6^f$</td>
<td>$-16.5$ to $-0.8$</td>
<td>0.37</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>$-8.6^f$</td>
<td>$-16.9$ to $-0.2$</td>
<td>0.36</td>
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<tr>
<td>Mental health</td>
<td>$-10.3^f$</td>
<td>$-16.7$ to $-3.9$</td>
<td>0.52</td>
</tr>
<tr>
<td>Vitality</td>
<td>$-9.3^f$</td>
<td>$-16.1$ to $-2.4$</td>
<td>0.46</td>
</tr>
<tr>
<td>General health perception</td>
<td>$-4.9$</td>
<td>$-11.6$ to $1.8$</td>
<td>0.24</td>
</tr>
<tr>
<td>Physical components summary</td>
<td>$-1.7$</td>
<td>$-4.8$ to $1.4$</td>
<td>0.19</td>
</tr>
<tr>
<td>Mental components summary</td>
<td>$-5.5^f$</td>
<td>$-9.1$ to $-1.8$</td>
<td>0.49</td>
</tr>
</tbody>
</table>

### Table 5. Association Between Repeat Revascularization and Health Status at 12 Months based on Longitudinal, Random Effects Growth Curve Models

<table>
<thead>
<tr>
<th>Health Status Measure</th>
<th>CABG Group</th>
<th>PCI Group</th>
<th>Effect Size*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Effect</td>
<td>95% CI</td>
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<tr>
<td><strong>Seattle Angina Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angina Frequency</td>
<td>$-11.2^f$</td>
<td>$-16.8$ to $-5.6$</td>
<td>0.79</td>
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<tr>
<td>Physical Limitations</td>
<td>$-13.3^f$</td>
<td>$-20.6$ to $-6.0$</td>
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<tr>
<td>Quality of Life</td>
<td>$-17.0^f$</td>
<td>$-24.8$ to $-9.2$</td>
<td>0.82</td>
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<tr>
<td>Treatment Satisfaction</td>
<td>$-3.7$</td>
<td>$-9.1$ to $1.8$</td>
<td>0.25</td>
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<tr>
<td><strong>36-item Short Form General Health Survey</strong></td>
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<tr>
<td>Physical Function</td>
<td>$-7.8$</td>
<td>$-16.3$ to $0.6$</td>
<td>0.32</td>
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<tr>
<td>Role Physical</td>
<td>$-6.8$</td>
<td>$-16.4$ to $2.8$</td>
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<tr>
<td>Role Emotional</td>
<td>$-12.4^f$</td>
<td>$-21.5$ to $-3.4$</td>
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<td>Social Function</td>
<td>$-7.1$</td>
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<tr>
<td>Bodily Pain</td>
<td>$-4.7$</td>
<td>$-13.7$ to $4.3$</td>
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<tr>
<td>Mental Health</td>
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<td>$-9.4$ to $4.1$</td>
<td>0.15</td>
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<tr>
<td>Vitality</td>
<td>$-10.4^f$</td>
<td>$-17.7$ to $-3.2$</td>
<td>0.53</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>$-7.2$</td>
<td>$-14.5$ to $0.1$</td>
<td>0.35</td>
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<tr>
<td>Physical Components Summary</td>
<td>$-2.6$</td>
<td>$-5.9$ to $0.7$</td>
<td>0.28</td>
</tr>
<tr>
<td>Mental Components Summary</td>
<td>$-3.8^f$</td>
<td>$-7.5$ to $-0.1$</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Abbreviations:** CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

*Mean effect in terms of the pooled standard deviation of the measure.

†$P<0.05$; ‡$P<0.01$; §$P<0.001$. 

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those treated with PCI. Similarly, in a single-center, observational study of 475 patients treated with CABG or PCI and followed for 12 months, restenosis requiring reintervention was highly predictive of worse health status, but patients treated with PCI without restenosis still had worse SAQ angina frequency, physical limitations, and quality-of-life scores than patients treated with CABG by 3 to 5 points, similar to the overall difference observed between the 2 treatments.

Both of these studies interpreted their findings as indicating that patients treated with PCI who required repeat revascularization accounted for much of the observed difference in health status between PCI and CABG; however, as the differences in angina frequency scores between patients treated with CABG and patients treated with PCI without restenosis were similar to those in the overall population in both studies, there appears to be an incremental antianginal benefit of CABG over PCI that cannot be explained fully by the differential need for repeat revascularization between the 2 procedures. Thus, even though recurrent ischemia leading to repeat revascularization remains an important determinant of health status after PCI or CABG, these previous studies lend support to our finding that differences in repeat revascularization explain only a modest proportion of the between-group health status benefits of CABG over PCI.

Potential Mechanisms
There are several potential explanations for our findings. It is possible that some patients treated with PCI may have experienced restenosis or disease progression during follow-up but were not felt to warrant repeat revascularization. Alternatively, some of the antianginal benefits of CABG might have resulted from mechanisms unrelated to relief of myocardial ischemia (eg, denervation, placebo effects). Support for this concept can be found in the angiographic substudy of the Bypass Angioplasty Revascularization Investigation trial. In this study of 270 patients randomized to PCI or CABG, who underwent routine angiography at 12-months of follow-up, the degree of ischemic myocardium was estimated by a myocardial jeopardy index (the sum of the estimated percentage of left ventricular myocardium distal to stenoses >50%). As expected, the myocardial jeopardy index was strongly related to angina status among patients treated with PCI; however, among those treated with CABG, there was no relation between angina status at follow-up and the
extent of ischemic myocardium. Although coronary angiography is not a perfect method of assessing the burden of ischemia, these findings provide additional insight as to the potential mechanism of antianginal benefit of CABG over PCI in the absence of restenosis and suggest that even if there were a perfect stent (ie, one with no restenosis), it might still be inferior to CABG in terms of angina relief owing to these other mechanisms.

**Implications for Future Studies**

Our finding that the association between repeat revascularization and follow-up anginal status differed substantially among patients treated with CABG versus PCI has potential implications for the assessment of the relative merits of these 2 treatment strategies. In a trial comparing 2 treatments, the clinical impact of the end points being measured is assumed to be comparable between the 2 groups (eg, a death in 1 group is the same as a death in the other group). If the end points are not equivalent between comparison groups with respect to how they are measured or their consequences, then the treatment comparison will be biased. Our analysis suggests that the association between repeat revascularization and both disease-specific and generic health status differs considerably after CABG versus PCI; as a result, inclusion of repeat revascularization as an end point in trials comparing CABG and PCI may have limited validity.

Of note, our observations in this regard are similar to those recently proposed by Teirstein.19 He suggested, on the basis of anecdotal observations, that differences in rates of repeat revascularization between patients treated with CABG versus PCI may reflect, at least in part, differences in angiographic suitability for repeat revascularization after CABG. Our finding of important differences in the health status of patients treated with CABG versus those treated with PCI who required repeat revascularization provides objective evidence to support this concept, as it suggests a different threshold for reintervention, depending on the patient’s prior revascularization procedure. Although the end point of repeat revascularization remains important as a measure of resource utilization after coronary revascularization, our findings suggest that it is not a reliable surrogate for recurrent angina or a fixed decrement in health status. As such, we believe that its inclusion as a component of a primary composite end point in future studies comparing PCI with CABG may not be appropriate. Given the different underlying clinical significance of repeat revascularization between the 2 groups of patients, other end points, such as death or health status, which would be of similar relevance to patients regardless of type of revascularization and are less likely to be biased by prior therapy, would seem more valid and appropriate for future treatment comparisons.

**Limitations**

Our study has several important limitations. First, this was not a prespecified analysis of the SYNTAX trial, and thus the findings should be considered exploratory in nature. Second, these results are limited to only the first year of follow-up after revascularization, and it is unknown whether these findings would extend past this time period. Finally, we were unable to account for all potential patient and clinical factors associated with patients’ health status, which could potentially lead to unmeasured confounding.

**Conclusions**

In conclusion, among patients with 3-vessel or left main coronary artery disease randomized to treatment with CABG or PCI with paclitaxel-eluting stents, patients who required repeat revascularization had substantially worse angina and quality of life over the first year of follow-up compared with patients who did not; however, differences between the 2 treatments in the need for repeat revascularization explained only a modest proportion of the antianginal benefit observed with CABG over PCI in the overall population. These findings suggest that some of the antianginal benefit of CABG may result from mechanisms unrelated to relief of myocardial ischemia. In addition, there was substantial variation in the strength of association between repeat revascularization and health status in patients treated with CABG as compared with PCI. Although repeat revascularization may still have value as a measure of resource utilization, our results suggest that this end point has a different clinical impact based on the original treatment and thus should play a limited role as an indirect measure of health outcomes between these 2 revascularization strategies.

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