Coronary revascularization is performed to reduce myocardial ischemia and its sequelae of death, myocardial infarction, and anginal symptoms. A successful procedure increases the patient’s quality of life, length of life, or both. Clinical trials of coronary revascularization should measure these outcomes to assess progress toward the goals of therapy. Death is an important and unequivocal outcome but, fortunately, is uncommon, and hence, very large studies are needed to assess differences in mortality. Myocardial infarction is also an objective outcome because it requires laboratory measures such as electrocardiography, biomarker levels, and imaging results, but it too is uncommon and can be assessed only in large trials. In contrast to these hard outcomes, angina is a symptom, and its subjectivity has made it less desirable to clinical investigators as an outcome measure. Angina can be measured using standardized approaches, however, and its effect on health status and quality of life has been quantified in many clinical trials.

In addition to these standard outcomes, repeat coronary revascularization has been adopted as an end point in many trials of percutaneous coronary intervention (PCI). Early balloon angioplasty procedures had high rates of restenosis and, consequently, of repeat revascularization procedures, typically another angioplasty. In the early 1980s, most interventional cardiologists accepted repeat procedures as an inevitable consequence of PCI because restenosis proved very difficult to tame, at least by using drug therapy. The disease process of restenosis could be measured using coronary angiography, but the angiographic measures were of uncertain clinical importance. Repeat revascularization became a simple proxy for “clinically important restenosis” that was easy to count as an outcome, so repeat coronary revascularization emerged as an end point in trials of treatments aimed at reducing restenosis, the Achilles heel of PCI.

It soon became apparent that repeat revascularization was problematic as an outcome measure. A second procedure might be needed to treat restenosis, but it might be used to treat an entirely different lesion. So, the concept of target vessel revascularization and even target lesion revascularization emerged. Even more concerning was the evidence that repeat PCI often was prompted by the appearance of the vessel, not by the patient’s symptoms or by objective evidence of myocardial ischemia. This phenomenon was documented quite rigorously when patients were randomized to receive a protocol coronary angiogram—there was a flurry of repeat procedures in the protocol angiography group subsequent to angiography, but no such procedures were seen in the clinical angiography group.1,2 The conclusion is unmistakable—repeat revascularization is a subjective end point that is due more to the vagaries of physician choice than to the disease process.

Despite its clear limitations, repeat revascularization has become a favored end point in PCI trials. The more serious outcomes of death and myocardial infarction are so uncommon that it is hard to design trials with sufficient statistical power to document reductions in these hard end points. The composite outcome of major adverse cardiac events (usually defined as death, myocardial infarction, or repeat revascularization) was devised to increase the number of outcome events and improve the power of clinical trials. Composite outcomes are problematic in general, but composites that include repeat revascularization are particularly problematic.3

Having a repeat revascularization procedure is hardly as bad as having a myocardial infarction, let alone dying, but each has the same weight in the composite major adverse cardiac events outcome. In addition, repeat revascularization events vastly outnumber the deaths and myocardial infarctions in any trial so that they become the primary driver of the composite end point.

The SYNTAX Trial

The investigators for the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial, which randomized 1800 patients with 3-vessel or left main coronary heart disease to coronary artery bypass graft (CABG) surgery or PCI using a drug-eluting stent,4 chose as the primary end point the composite outcome of death, myocardial infarction, stroke, or repeat revascularization in the 12 months following the initial revascularization. The primary end point was less frequent in the CABG group than in the PCI group (12.4% versus 17.8%, \( P=0.002 \)). This result was driven almost entirely by a lower rate of repeat revascularization in the CABG group (5.9% versus 13.5%, \( P<0.001 \)) because rates of death, myocardial infarction, or stroke were almost identical (7.7% versus 7.6%, \( P=0.98 \)). The investigators also collected information about the disease-specific and general health status of the participants in the trial using the Seattle Angina Questionnaire, Medical Outcomes Study 36-Item Short-Form
Health Survey, and the European Quality of Life-5 Dimensions instrument. Overall, patients assigned to CABG had significantly less angina at 6 and 12 months of follow-up, although the absolute differences in angina frequency were small (76.3% versus 71.6% angina free at 12 months, \( P=0.05 \)). These results are broadly consistent with the results of prior trials of CABG and PCI.

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Arnold and colleagues assess the effect of repeat revascularization on angina and health status. They used a random-effects growth curve model to define clinical predictors of disease-specific and general health status among patients in the SYNTAX trial over 12 months of follow-up. Despite the relative short follow-up period, the longitudinal analysis provides several important observations.

Patients who underwent repeat revascularization during follow-up had more frequent angina (and, hence, lower Seattle Angina Questionnaire angina frequency scores) at 6 and 12 months than patients who did not require repeat revascularization. This finding is what one would expect to see: Patients with greater residual or recurrent ischemia experience more angina and are more likely to undergo diagnostic angiography and subsequent revascularization.

The most important insight of this analysis by Arnold and colleagues comes from comparing, by treatment group, patients who required revascularization with those who did not. The difference in the angina frequency score at 6 months between patients who required repeat revascularization and those who did not was substantially greater in the CABG group (mean difference, 19.8 points) than in the PCI group (mean difference, 8.5 points). This observation suggests that patients had to experience more severe symptoms after CABG before they underwent repeat revascularization. Although it is possible that patients who had recurrent angina after CABG were less likely to have anatomy amenable to repeat revascularization, it is more likely that physicians simply had a higher threshold for recommending repeat revascularization after CABG than after PCI. This subjective component, a differential referral pattern for revascularization based on the preceding revascularization procedure, introduces a bias in the use of repeat revascularization as an end point when comparing CABG with PCI.

### Implications

The observations from the SYNTAX trial underscore the limitations of repeat revascularization as an end point in clinical trials. A repeat procedure can be a response to symptoms, an angiogram, or both. The threshold for performing a repeat procedure varies among patients (higher after CABG and perhaps in older patients) and almost certainly varies among physicians. Repeat revascularization is costly and inconvenient, but as an end point, it does not measure progress toward the goals of treatment, which are a reduction of symptoms, permanent complications, and death.

Although repeat revascularization is an extremely relevant consideration when comparing clinical strategies, it is a subjective and biased outcome. It does not belong in a composite primary outcome measure in comparative effectiveness trials of PCI.

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Dr Kazi reports no conflicts. Dr Hlatky has served as a consultant to Gilead and lists all his relationships with industry at http://med.stanford.edu/profiles/Mark_Hlatky.

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