Although percutaneous coronary intervention (PCI) for unprotected left main stenosis is a controversial subject today, it has a remarkably long history in the field of coronary intervention. In fact, in the very first published description of balloon angioplasty in *The Lancet* in 1978, two of the first five cases reported by Gruentzig were of left main lesions. The illustration in the original *Lancet* description of percutaneous transluminal coronary angioplasty using simple balloon technology was a midshift focal left main lesion.

Since then, the database on left main intervention has consisted largely of single-center series involving protected or high-risk left main patients. The largest nonrandomized report of PCI outcomes for unprotected left main lesions using current approaches of stenting was reported by Seung and compared 3-year outcomes in patients treated with stents for left main disease with a propensity-matched group undergoing coronary artery bypass graft surgery (CABG). In this study of more than 2,000 patients, the cumulative incidence of death, myocardial infarction, or stroke was statistically equal in the two groups of patients after 3 years. A 10% excess of repeat revascularization procedures in the left main PCI group was noted. The study included patients treated with both bare-metal and drug-eluting stents (DES). The risk of target vessel revascularization was decreased by half with DES compared to bare-metal stents. This difference in repeat revascularization between PCI and CABG therapy is an important focus of discussion regarding the utility of PCI for left main disease.

**THE SYNTAX TRIAL**

Recently, the randomized SYNTAX trial was reported, including patients with left main and/or three-vessel coronary artery disease. Patients were randomized to undergo PCI with DES compared to CABG. The SYNTAX study is unique in that there were no specific inclusion or exclusion criteria other than consensus by the surgeon and interventional cardiologist that the patient’s anatomy was suitable for either approach. SYNTAX thus reflects a real practice population and is the largest randomized comparison of PCI with DES and CABG.

The 12-month outcomes of the entire group of both left main and three-vessel disease patients showed no differences in all-cause mortality or myocardial infarction (Figure 1). There was a significant excess of stroke in the CABG group and an excess of repeat revascularization of approximately 8% in the patients treated with DES. The predetermined endpoint for the trial was the....

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**Figure 1.** Endpoint outcomes to 12 months for the overall SYNTAX population. All-cause mortality and myocardial infarction are statistically not different. There is an excess of stroke in the CABG group and an excess of repeat revascularization in the PCI group.

**Figure 2.** MACCE out to 12 months for the overall SYNTAX patient population. The difference in overall adverse events is driven by repeat revascularization and does not demonstrate noninferiority, the primary SYNTAX trial endpoint, for the PCI group.
combination of death, myocardial infarction, stroke, and repeat revascularization (major adverse cardiac and cerebrovascular events—MACCE). The PCI group did not achieve noninferiority to CABG for the combined MACCE endpoint. The MACCE endpoint is driven by the excess in repeat revascularization in the PCI group (Figure 2). The gap between PCI and CABG in this trial was less than 8% for the overall population, despite coronary anatomy complexity and numbers of stents used per patient that exceed any previous revascularization trial. In context, the repeat revascularization gap has been decreasing steadily as technology and techniques improve, even when taking on increasingly complex coronary disease (Figure 3).

In the left main disease subset of patients, the outcome for all-cause mortality and myocardial infarction was equivalent at 12 months. However, an excess in stroke was noted in the CABG group (Figure 4). Importantly, the difference in repeat revascularization was smaller when comparing DES with CABG in the left main subset than in the three-vessel disease group (Figure 5). Furthermore, when the left main subset was stratified according to the severity of overall coronary disease complexity using the SYNTAX score, patients with low and intermediate tertile SYNTAX scores had outcomes that were as good as or numerically better than patients who underwent bypass surgery (Figure 6). Although MACCE rates were higher in diabetic patients for both PCI and CABG, there was still little difference among diabetic patients when PCI and stents were compared, especially in the lower two tertiles of SYNTAX score. Two-year data in the left main group show no differences in the combined incidence of death, stroke, and myocardial infarction, and no difference in overall MACCE. A difference of approximately 6% in excess repeat revascularization was seen in the PCI group, without consideration of the SYNTAX lesion complexity score.

A critical question is whether all the elements of the combined endpoint of MACCE make sense being grouped together. The components of the endpoint are all-cause mortality, myocardial infarction, stroke, and repeat revascularization. The clinical importance and severity of death, myocardial infarction, and stroke are clearly different than repeat revascularization. Some trials have used the first three components (death, myocardial infarction, and stroke) as a primary endpoint. Had this been the prespecified endpoint in SYNTAX, the interpretation of the outcome of the trial could be very different. The major distinguishing feature between bypass surgery and stent therapy in the majority of patient subsets is excess repeat revascularization with PCI, which does not have the acute or long-lasting clinical impact of death, myocardial infarction, or stroke. It is important to consider the differences in MACCE component severity when interpreting the SYNTAX trial.

Another important consideration is the quality of life and cost outcomes in the trial. These were reported at the American College of Cardiology meeting in 2009.5 The cost effectiveness of CABG versus PCI in the overall population favored stent therapy (Figure 7). The difference favoring PCI was greatest in the patients in the lower two tertiles of SYNTAX score. Higher costs and worse outcomes overall were seen in the CABG group. In addition to the lower cost of stent therapy, this is obviously driven by diminished quality of life during the first several months after surgery due to the greater difficulty of recovery from that procedure.
One of the major arguments favoring surgery for patients with multivessel coronary artery disease is a better outcome in terms of long-term survival noted in the previous Bypass Angioplasty Revascularization Investigation (BARI) trial. In the BARI trial, the survival difference between CABG and percutaneous transluminal coronary angioplasty began to appear only after approximately 3 years of follow-up. It is critical to note that this trial was performed in the era of “plain old balloon angioplasty” without the aid of stents. BARI has important historical interest but does not reflect outcomes in the stent era. For example, in the BARI trial, approximately 10% of PCI patients required revascularization during the index hospitalization due to acute failure of angioplasty. This is not an outcome that is seen in the stent era.

Meta-analyses of previous trials comparing PCI and CABG have reported no differences in survival up to 10 years after stent therapy. A meta-analysis of 23 randomized clinical trials that included approximately 10,000 patients showed no mortality difference between PCI and CABG at 5 and 10 years, despite the inclusion of trials from the prestent, plain balloon angioplasty era. A more contemporary meta-analysis using patient-level data from the ARTS, ERACI-II, MASS-II, and SOS trials also found no differences in overall survival out to 5 years after initial treatment. The combined freedom from death, stroke, and myocardial infarction was similarly identical out to 5 years. The gap in repeat revascularization between PCI and CABG after 5 years was 21% in this meta-analysis.

The 1-year SYNTAX results show good PCI results in left main patients with the lower two-thirds of disease complexity characterized by SYNTAX score. Some important trial details must be considered to understand the impact of the results of SYNTAX. The SYNTAX trial involved the most complex coronary artery disease ever encountered in a stent experience. The mean stented length was 86 mm, and one-third of the patients received more than 100 mm of stented length. Three-quarters of the patients had bifurcation lesions, and almost one-quarter had chronic total occlusions. In the context of this high level of anatomic complexity, the most complex patients appear to be the only group in whom major
events are more common with PCI than with CABG. The lower two tertiles of SYNTAX score had results that were as good as CABG statistically, and in some cases, were numerically better. It is this group that we have realistically considered a target population for unprotected left main stenting.

A practical guide to assessment of patient complexity may be an estimate of the number of intended stents. The lowest tertile of SYNTAX score is represented by scores of zero to 22, and the middle tertile is represented by scores of 23 to 32. The mean number of stents in the overall SYNTAX trial was 4.6 per patient. In our experience, intended placement of more than seven stents defines the upper third of lesion complexity or SYNTAX score. Patients with lower scores, in whom one to four stents are expected, may represent an ideal population for inclusion in stent therapy for unprotected left main disease. Those in whom seven or fewer stents are expected are likely to fall into the middle tertile and are often good candidates for PCI. What proportion of the de novo left main population does this represent? In the SYNTAX population of left main and three-vessel disease patients, one-third had left main disease. Of the left main group, one-third had isolated left main disease or left main with one-vessel disease, and another third had left main with two-vessel disease. Thus, approximately 10% of this overall population had isolated left main or left main with one-vessel disease, and another 10% had left main with two-vessel coronary disease.

What is usual practice in the community today? Before the SYNTAX trial began, a survey was done of possible study sites. The interventional cardiology and cardiothoracic surgery units at each site completed a Web-based survey, which collected data on left main and three-vessel disease patients over a retrospective 3-month period. The survey captured 12,158 patients. Approximately 25% of the total group and 33% of the left main patients were treated with PCI. European operators were three times more likely to perform PCI for unprotected left main lesions than North American operators. This was the practice prior to the beginning of the SYNTAX trial and before some of the larger non-randomized trial data were reported. Thus, PCI for left main and three-vessel disease was commonly performed several years ago. Practice and published guidelines are discordant. Society guidelines still categorize PCI for unprotected left main disease in good surgical candidates as class III, and this was reaffirmed in the recently published appropriateness criteria document.

CONCLUSION
Randomized trial results from SYNTAX comparing PCI with DES to CABG for unprotected left main disease demonstrate good outcomes in patients with relatively simple coronary anatomy, characterized by SYNTAX scores in the lower two tertiles. The outcome in terms of death and myocardial infarction is not different in PCI compared to CABG, stroke is less frequent with PCI, and repeat revascularization in the lower score groups is similar. In our practice, these patients have a discussion with both the interventional physician and the cardiac surgeon (Figure 8). An individualized decision, largely guided by the SYNTAX score, is made regarding the mode of revascularization. For many patients with left main disease, PCI has not previously been considered, and an important subset now have PCI as an option for therapy.

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