Is surgery or percutaneous revascularization the preferred strategy for patients with significant left main coronary stenosis?

Surgery, Not Percutaneous Revascularization, Is the Preferred Strategy for Patients With Significant Left Main Coronary Stenosis

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The place to begin is with a brief discussion of the general case: percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) for all anatomic varieties of coronary disease. Daemen et al1 pooled 3051 patients from 4 randomized trials comparing CABG with PCI using bare metal stents (BMS). At 5 years, PCI and CABG were similar with respect to death, myocardial infarction (MI), and stroke. Repeat revascularization was significantly more frequent after PCI (29.7% versus 7.9%; \( P<0.001 \)), which probably accounted for a significantly higher frequency of major adverse cardiac and cerebrovascular events (MACCE) after PCI (39.2% versus 23.0%; \( P<0.001 \)). Revascularization was considered complete in 89.4% of CABG patients compared with 62% of PCI patients (\( P<0.001 \)). Bravata et al2 reviewed 23 randomized controlled comparisons of CABG with PCI using bare metal stents (BMS) and found significantly greater angina relief with CABG at 1 to 5 years (\( P<0.001 \)). Repeat revascularization was more frequent after PCI (risk difference 25% at 1 year and 33% at 5 years; \( P<0.001 \)). Javaid et al3 reviewed their “real world” experience with CABG and PCI using drug-eluting stents (DES) for 2- and 3-vessel coronary disease in 1680 patients and found that MACCE were more frequent with PCI (21.2% versus 9.7% for 2-vessel disease; \( P<0.001 \); 28.4% versus 10.8% for 3-vessel disease; \( P<0.001 \)).

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The broad experiences reviewed above include experience with BMS and DES and contain a very small number of patients with left main coronary artery (LMCA) stenosis. Do the same lessons apply? Early reported experience focused on the LMCA population varied widely. In the discussion that follows, DES were used exclusively or partially unless specifically stated otherwise. In 50 patients followed up for 5.2 months, with angiography in 42%, target lesion revascularization was an encouraging 6%.4 In another series of 50 patients followed up for 9.2 months, with 98% angiography, target lesion revascularization was a startling 38%.5 More recently, Takagi et al6 contributed a meta-analysis of 6 comparative studies published from 2006 to 2008,4,7–11 including 1 randomized trial. Small, nonsignificant trends favored PCI over CABG with respect to death and MACCE (Figures 1 and 2). As in essentially all comparisons of PCI with CABG, however, CABG was significantly superior to PCI with respect to repeat revascularization (Figure 3). Importantly, follow-up was relatively short, ranging from 6...
months to 3 years, which clearly prevents full appreciation of the impact of a difference in durability on more critical end points.

Idiosyncrasies of the trials in the Takagi meta-analysis deserve comment. In the randomized trial reported by Buszman et al, only 72% of surgical patients received internal mammary grafts, a strikingly low figure when essentially 100% of the patients in the cohort (unprotected LMCA disease) required a bypass to the left anterior descending artery (LAD). This might help to explain why 5 of 53 (9.4%) in the CABG group required repeat revascularization (left main PCI plus other PCI) by 1 year. In comparing treatment groups, the authors prefer to mention that only 5 of 52 (9.6%) in the PCI patients required repeat left main PCI rather than compare total repeat revascularization, for which the difference between groups was significant (9.4% versus 29%; \( P = 0.01 \)), information that is relegated to the footnote of a table. Much is made of “significant” difference in left ventricular ejection fraction at 1 year, when left ventricular ejection fraction was 58.0% in the PCI group and 54.1% in the CABG group (\( P = 0.01 \)). It is hard to imagine that a 3.9% difference in left ventricular ejection fraction is clinically meaningful or reproducible.

Also included in the meta-analysis is a remarkable series from Korea, “where stenting of the left main coronary artery has been more common practice than in Western countries.” This behavior allowed Seung et al to assemble a large series of patients with unprotected LMCA disease in which patient and physician preference sorted the population into 2 roughly equal groups (1102 PCI, 1138 CABG), and, in marked contrast to many other series, only 2.6% of the PCI group were labeled “poor candidates for surgery.” Although this produces a unique glimpse of real-world behavior, interpretation teeters on the ability of propensity analysis to balance selection influences. The propensity-matching challenge is nontrivial when the CABG group is significantly older, with lower ejection fraction, and has a significantly higher prevalence of diabetes mellitus, hyperlipidemia, smoking, history of infarction, peripheral vascular disease, presentation with unstable angina, distal-bifurcation disease, 3-vessel disease, and right coronary involvement. Follow-up was a commendable 3 years, at which point the only significant hazard ratios, ranging from 4.76 to 10.70 (\( P < 0.001 \)), demonstrated increased risk of target vessel revascularization for PCI compared with CABG. Represented graphically (Figures 4 and 5) in the propensity-matched cohorts, BMS were inferior to DES, but both were inferior to CABG (\( P < 0.001 \)).

Two recent series not included in the Takagi meta-analysis deserve mention. Sanmartin et al compared results in 96 PCI patients with 245 CABG patients treated between 2000
and 2005. Selection was based on “careful individual case analysis.” At 30 days, MACCE (death, Q-wave infarction, stroke, and repeat revascularization) favored PCI (2.1% versus 9.0%; \( P < 0.03 \)), which is typical of any such comparison focused on the first 30 days. At 1 year, MACCE rates were similar because of significantly (\( P < 0.02 \)) higher repeat revascularization in the PCI group. Angiographic follow-up was both scheduled and symptom driven and was obtained in only 57% of the PCI group, which might have contributed to a relatively low rate of repeat revascularization (5.2%) compared with most series. In a more limited analysis, Brener et al.\(^{13} \) compared 97 PCI patients with a retrospectively matched group of 190 CABG patients and found comparable mortality at 3 years. Angiographic follow-up was obtained between 3 and 6 months in 64 PCI patients, and only 3 needed repeat revascularization. The authors claim to be describing “long-term outcomes,” a euphemism forgivable in PCI literature.

The latest word on the subject comes from oral presentation of the SYNTAX trial (SYNergy between PCI with TAXus and Cardiac Surgery) at the European Society of Cardiology meeting on September 1, 2008.\(^{14} \) Designed to be an “all-comers, real world” trial combining a randomized arm with 2 nested registries comparing PCI with CABG, 85 international sites randomized 897 patients to CABG and 903 patients to PCI with paclitaxel stents, followed for 12 months, and including 705 LMCA patients. The good news for PCI was that PCI and CABG did not differ significantly with respect to all-cause death, MI, graft occlusion/stent thrombosis, or a combination of all-cause death/cerebrovascular accident/MI. Cerebrovascular accident was more frequent in the CABG group (2.2% versus 0.6%; \( P < 0.003 \)). The bad news, once again, was that repeat revascularization was significantly more frequent in the PCI group (13.7% versus 5.9%; \( P < 0.0001 \)). Because the primary end point for the trial was MACCE at 12 months, and MACCE included repeat revascularization, the trial failed to prove the noninferiority of PCI to CABG. Because the primary end point was not met, LMCA and other subgroup comparisons are rendered observational, which is extremely unfortunate for the subject at hand. MACCE rates for subgroups varied from small differences (13.7% CABG versus 15.8% PCI for all LMCA variants) to larger differences (11.5% CABG versus 19.2% PCI for all 3-vessel disease). At best, the long-anticipated results from SYNTAX imply tolerable safety for LMCA PCI and for PCI in general, but the taint of repeat revascularization associated with PCI remains.

Moving now to a mixture of evidence and speculation, let us consider 3 reasons that PCI of the LMCA might be technically easier and more successful than PCI in other parts of the coronary circulation and therefore more competitive with CABG. First, it is certainly logical that the large diameter of the LMCA might promote patency. No matter how much the stent, as well as the healing phenomena associated with it, adds to the inner diameter of a vessel, the cross-sectional area will be reduced less in a larger vessel. Second, proximal location is also potentially advantageous because fewer potential complications of wire transit present themselves, both getting in and getting out. Third, patients with isolated LMCA stenosis might require fewer stents than...
patients with more complex LAD and circumflex disease. That fewer stents might be beneficial is not pure speculation: Chu et al\textsuperscript{15} found significantly decreased survival ($P<0.0001$) in patients receiving $\geq 3$ sirolimus-eluting stents compared with those receiving single stents. Even with these theoretical advantages, however, the short length and branching complexity of the LMCA add major disadvantages. Substantial evidence exists that PCI involving branches and bifurcations has imperfect results and presents distinct challenges that are unresolved.\textsuperscript{16–22} The sheer number of vivid technical labels (eg, kissing, culotte, crush) associated with bifurcation stenting suggests an unsolved problem. The left main coronary bifurcation is the ultimate branch point in terms of potential hazards, even more so in the 10% to 15% main coronary bifurcation, even less if it is not placed at a trifurcation. Valgimigli et al\textsuperscript{24} found significantly higher probability of major adverse cardiac events in patients with distal LMCA disease (30%) versus those with “nondistal” LMCA disease (11%), with a hazard ratio of 3.42 ($P=0.007$) for distal involvement (Figure 4). Suppose we accept that stenting of the ostium and shaft of the LMCA is more reproducible than stenting of the bifurcation. Even so, the LMCA averages only 10 mm in length (range, 1 mm to 30 mm),\textsuperscript{25} and the shortest stents available are 8 mm. Therefore, the shortest possible ostial/shaft stent, unless it protrudes into the aorta, will have a mere 2 mm of clearance from the average bifurcation, even less if it is not placed perfectly flush with the ostium. In the 6 series summarized in the Takagi meta-analysis,\textsuperscript{4,7–11} 49% to 89% of the patients in each series had distal LMCA stenosis, or 58% of the entire combined cohort (903/1566). Frequent and predictable avoidance of the challenges associated with the bifurcation is anatomi- cally unlikely.

But what about the tried-and-true surgical alternative? CABG earned its designation as the gold standard for treatment of LMCA disease many years ago. The American College of Cardiology/American Heart Association guidelines recognize only CABG as having a class IA indication for treatment of LMCA disease, regardless of symptoms or presentation.\textsuperscript{26} PCI has class II indications only.\textsuperscript{27} Nevertheless, surgery is still... surgery. No one actively desires an operation, and no one should, unless the benefits outweigh the risks. The risks are well documented; the Cleveland Clinic reported 2.3% in-hospital mortality and 11.3% mortality at 1 year in a cohort of patients with LMCA disease.\textsuperscript{28} For low-risk patients in the same cohort, 1-year mortality was 5.7%. The benefits have been clear for decades,\textsuperscript{29–32} most notably a 25% improvement in mortality between 5 and 10 years compared with medical treatment. It is obvious that nonsurgical options have improved dramatically in 30 years. Although this is certainly true and has shifted the standard against which surgery should be compared, surgery has not stood still. In the Coronary Artery Surgery Study,\textsuperscript{29} the internal mammary was used in only 9.5% of patients, and perioperative mortality was 4.6%. In contrast, more recent, single-center observational series strongly reliant on arterial conduits report 2% to 5% mortality at 5 years and 10% mortality at 10 years,\textsuperscript{33–35} with 95% angiographic graft patency at 1 year.\textsuperscript{33} As PCI entered the picture, comparisons with CABG were inevitable and appropriate. As we learned in the first paragraph above, meta-analyses, not focused exclusively on LMCA disease and including experience with both BMS and DES, have typically shown advantage for CABG that increases with length of follow-up.\textsuperscript{1,2,36} (Figure 5), particularly in 2- and 3-vessel disease involving the proximal LAD.\textsuperscript{37} (Figure 6). Innumerable observational series, and a much smaller number of randomized trials, have shown variability with respect to major outcomes, in part because most comparisons of CABG with PCI have markedly unbalanced risk profiles favoring PCI, as illustrated by the Korean series\textsuperscript{39} detailed above, leaving it to propensity analysis and other statistical gymnastics to engineer a fair comparison. With very few exceptions, however, CABG has been significantly superior to PCI with respect to repeat revascularization and target lesion revascularization in particular, just as the LMCA series described above have shown. Are there consequences? Van Belle et al\textsuperscript{38} found significantly reduced survival ($P<0.0001$) in patients after PCI who developed occlusive stenosis in a series with an average of 6.5 years of follow-up (Figure 7). In the New York State database, repeat revascularization and mortality were significantly increased in the BMS PCI cohort at 3 years.\textsuperscript{39} More recently, these findings were confirmed in a comparison of DES PCI with CABG in the same database at 18 months.\textsuperscript{40} Repeat revascularization is not benign.

Opponents of this point of view will quickly assert that vein grafts are no guarantee against repeat revascularization.
This is absolutely true. Always mentioned in this context is the Project of Ex Vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial, in which an astonishing 45% of vein grafts failed between 12 and 18 months, retiring the trophy for poor vein graft results. In contrast, a very large series reported from the Cleveland Clinic found 22% vein graft failure at 1 year, which is half the frequency reported in PREVENT IV. A very recent series from another institution observed 14% vein graft failure at 5 years. Seventy-seven percent of the patients in this series were assessed with angiography, which compares favorably with 80% in PREVENT IV. In other words, in these 23 trials, by 5 years PCI was no better than the worst vein graft results ever published (PREVENT IV). Whatever the benchmark for vein graft failure may be, vein grafts are not the Achilles heel of CABG for LMCA because a surgeon facile with bilateral internal mammary bypasses can usually revascularize the entire LMCA distribution without using any other conduits.

Two years ago, in this journal, Kereiakes and Faxon wrote a thorough and thoughtful editorial titled “Left main coronary revascularization at the crossroads” and concluded, “We believe that the current practice of unprotected LMCA stenting with current DES platforms is highly variable and should be prudent and constrained. . .only patients at increased risk for CABG and those who refuse to undergo CABG should be considered.” Not much has changed since 2006. PCI is competitive with CABG at 3 years with respect to mortality and certain composite end points. This is a blow to surgeons who consider PCI of the LMCA irresponsibly hazardous and is not a trivial achievement considering that Grünzig et al described “sudden and serious” complications when treating LMCA lesions with balloon angioplasty. However, durability of the result with PCI is markedly and persistently inferior to CABG. Why might this be true now and in the future? Despite the theoretical advantages PCI might enjoy in the LMCA, it still involves placing a foreign body in a segment of the coronary tree that is prone to atherosclerosis, a foreign body often containing a drug in a polymer. It is assumed that the sum of all potential effects of the drug and polymer on vascular healing and remodeling is net positive, but this is unknown. Add to these features the high frequency of bifurcation involvement, and the aforementioned results for PCI seem all the more remarkable. One can only admire the optimism of interventionalists who celebrate successful repeat PCI treatment of LMCA PCI failures, as if repeat PCI guarantees long-term success. Contrast this with CABG, in which an artery that rarely has significant athero-

Figure 6. The 95% CI for Ln (adjusted hazard ratio) of CABG patient death and percutaneous transluminal coronary angioplasty (PTCA) patient death within a 3-year period (excluding patients with M < 24 hours before procedure). Results for percutaneous transluminal coronary angioplasty are before the use of DES. LAD indicates left anterior descending artery; Prox, proximal. Reproduced with permission from Hannan et al. Copyright © 1999, the American College of Cardiology.

Figure 7. Kaplan-Meier survival curves for long-term mortality as a function of vessel patency at repeated angiography in dilated vessels after percutaneous transluminal coronary angioplasty. Follow-up of 513 patients at a mean of 6.5 ± 2.4 years after follow-up angiography is shown. Actuarial 5- and 10-year mortality rates were 13% and 24% in patients without restenosis, 23% and 35% in patients with nonocclusive restenosis, and 38% and 59% in patients with coronary occlusion. Results are before use of DES. Used with permission from Van Belle et al. Copyright © 2001, the American Heart Association.
sclerosis is connected to the most normal part of the LAD or circumflex, usually without disturbing native inflow to the conduit. How can durability not be superior and a fair tradeoff for the increased acute risk inherent in operation? It is customary to add to all discussions of this subject that better resolution of the options awaits the results of randomized controlled trials. The long-awaited results of SYNTAX have been described above and do not push the pendulum toward PCI. Other trials are incomplete or in the planning stage. Be those as they may, the device development pipeline will keep flowing. Stent X will be ready to go, propelled by outstanding results in swine, demanding new trials. Scaffolding Y, armed with drug X in novel polymer Z, will already have a waiting list of eager farm animals dying to try the latest technology. CABG, meanwhile, will be plodding along, using a few strands of polypropylene and some sternal wire, and in fair, long-term comparisons, it will be hard to beat.

Disclosures

Dr Smith is an investigator in the FREEDOM trial, a multicenter, international trial comparing PCI to coronary bypass in diabetic patients with multivessel disease, for which he receives no financial support. He is also the surgical principal investigator in the PARTNER trial, a multicenter, international trial comparing percutaneous aortic valve implantation to conventional aortic valve replacement, sponsored by Edwards LifeSciences. He is reimbursed by Edwards for travel and implantation to conventional aortic valve replacement, sponsored by Edwards LifeSciences. He receives no financial support. He receives no financial support.

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Response to Smith

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Dr Smith’s excellent review contains the following central arguments: (1) Repeat revascularization rates consistently favor coronary artery bypass graft (CABG). I agree, but, as highlighted in my article, the “revascularization gap” has narrowed, and revascularization by percutaneous coronary intervention (PCI) is a minor event in the life of most patients. Fundamentally, a patient who chooses PCI for unprotected left main disease must be comfortable with the possibility of repeat PCI. (2) The length of follow-up in recent unprotected left main disease studies is insufficient. Although I agree that longer follow-up is needed, I am doubtful that longer follow-up will change my view. Even if longer-term follow-up reveals statistically improved survival in CABG patients, the clinical significance will be small given the large number needed to treat. I stand by my position that subjecting a large number of patients to the hazards of CABG (often not measured in the traditional major adverse cardiac events end point) instead of a far simpler PCI does not provide a favorable risk-reward ratio. (3) PCI techniques are still evolving, whereas the “tried and true” CABG remains the gold standard. Sadly for CABG, Dr Smith is correct. My response is to passionately argue for evolution of the CABG procedure. Why do <10% of patients in the United States receive bilateral arterial grafts despite their documented benefit? Why haven’t less invasive grafting techniques advanced further? Dr Smith reports that “not much has changed since 2006.” I submit that stenting techniques have changed tremendously in response to a tidal wave of new data and the shared experiences of a highly networked cardiology community. This evolution is precisely why unprotected left main stenting now challenges CABG. I challenge my surgical colleagues to aggressively investigate and disseminate new surgical techniques. Ultimately, a hybrid approach with true minimally invasive arterial grafting of the left anterior descending coronary artery plus stenting of the remaining vessels may provide optimal revascularization.
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