EDITORIAL COMMENT

Left Main Drug-Eluting Stents
Natural Progression or a Bridge Too Far?*

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The left main coronary artery (LMCA) is arguably the most important inch-long structure in the human body, typically providing the blood supply for 75% or more of the myocardium. Occurring in approximately 9% of patients undergoing coronary angiography (1,2), symptomatic atherosclerotic disease of the LMCA managed conservatively (without revascularization) portends a dire prognosis, with up to a 20% 1-year and 50% 7- to 10-year mortality (3–7). Numerous registries and 2 randomized trials have demonstrated a marked survival advantage of coronary artery bypass graft (CABG) surgery over medical therapy in most subsets of patients with LMCA disease (5–7). Although performed decades ago, these studies continue to define the accepted standard of care for patients with obstructive LMCA disease. Nonetheless, the significant morbidity and mortality of CABG, as well as the high rate of saphenous vein graft attrition (which are still used in the majority of CABG procedures), has prompted the exploration of lesser invasive therapies.

On first impression, the LMCA might be considered an attractive target for percutaneous coronary intervention (PCI); lesions in the LMCA are short, proximally located, and readily crossed with a guidewire and balloon. Indeed, PCI of the LMCA was first proposed by no one less than Andreas Grüntzig (8), who performed balloon dilatation of an unprotected LMCA as 1 of his first 5 angioplasty procedures. While many early practitioners cautiously experimented with LMCA intervention, Geoffrey Hartzler and colleagues (9) at St. Luke’s Hospital in Kansas City exposed the limits of 1980s technology, documenting a high rate of procedural death (9.4%) and mortality at 3 years (64%) after LMCA balloon angioplasty, with restenosis often manifesting as sudden cardiac death. After this report, the enthusiasm for angioplasty as treatment modality for the diseased LMCA rapidly waned.

With the introduction of the bare-metal stent (BMS), LMCA intervention was resurrected. By preventing acute and chronic recoil and sealing dissection planes, coronary stents allowed more favorable PCI results to be obtained. Steve Ellis coordinated the ULTIMA (Unprotected Left Main Trunk Intervention Multicenter Assessment) registry (10), examining the outcomes of 279 patients undergoing PCI of unprotected LMCA lesions (those without the “protection” of a patent bypass graft conduit to either the left anterior descending or left circumflex artery) between 1993 and 1998 at 25 hospitals (69% with stents). Procedural mortality still occurred in 13.7% of patients, increasing to 24.2% at 1 year. However, 46% of patients in this series were deemed inoperable. Among 89 low-risk patients (age <65 years, left ventricular ejection fraction [LVEF] >30%, and no shock), there were no periprocedural deaths, and survival at 1 year was 96.6% (10). Other centers subsequently demonstrated favorable results in stable patients with preserved left ventricular function (11–13). Nonetheless, restenosis rates remained high, especially with involvement of the distal bifurcation, and direct comparisons with CABG were avoided.

By reducing neointimal proliferation after medial injury, drug-eluting stents (DES) markedly reduce restenosis and improve long-term event-free survival compared with BMS in noncomplex lesions in patients with stable coronary artery disease (14,15). Although LMCA lesions were excluded from the pivotal randomized trials leading to the U.S. approval of sirolimus-eluting and paclitaxel-eluting stents (14,15), their use in this setting has subsequently been cautiously explored (16–21). The results of these registry investigations have varied greatly (reflecting differences in patient selection, coronary anatomy, and technique), with reported restenosis rates ranging from 7% to 44%, and mortality at 6 to 12 months occurring in 0% to 11% of patients (16–21). While the reintervention rates after DES for LMCA angioplasty in these series are reduced compared with what the same investigators previously achieved with BMS, the use of historical control groups makes definitive conclusions problematic.

This issue of the Journal contains what will be memorized as an important piece of left main history, the first randomized trial comparing DES and BMS for LMCA intervention (22). Erglis et al. (22) prospectively randomized 103 patients at a single center with significant stenosis of the LMCA to BMS or paclitaxel-eluting stent implan-
tation, utilizing cutting balloon predilation (to improve lesion compliance) and intravascular ultrasound guidance to optimize procedural results. Of note, 77 patients (75%) had involvement of the distal bifurcation, but only 2 patients received multiple stents. Strikingly, no in-hospital deaths occurred, and there were only 2 deaths (1.9%, 1 in each group) at 6 months, with no episodes of stent thrombosis. Repeat revascularization procedures for recurrent angina or ischemia were required at 6 months in 8 BMS patients compared with 1 DES patient (16.0% vs. 1.9%, p = 0.01), a benefit attributable to a marked reduction in angiographic restenosis with the paclitaxel-eluting stent (22.0% vs. 5.7%, p = 0.02).

Do these results justify considering DES as a valid alternative to CABG for the majority of patients with LMCA disease? Numerous unanswered questions must be addressed before that bridge can be crossed. Can the favorable DES results of Erglis et al. (22) be replicated in a larger, multicenter experience? Are cutting balloon predilation and intravascular ultrasound guidance necessary? What is the best technique to manage complex disease at the distal left main bifurcation (1 vs. 2 stents, and if 2, T-stenting vs. V-stenting vs. crush stenting vs. culotte)? Is there a preference between the currently available DES for LMCA lesions, or will outcomes be optimized by emerging specialty stents designed for the distal bifurcation? Should routine surveillance angiography be performed to detect asymptomatic restenosis? What is the late safety profile of DES in the LMCA, and what is the optimal chronic antiplatelet regimen (i.e., for how long is clopidogrel required)? How are the results impacted by concomitant multivessel disease, left ventricular dysfunction, diabetes, and/or renal insufficiency? Most importantly, how do the results compare with CABG?

One small (105 patient) unpublished randomized trial of stenting (DES or BMS) versus CABG in patients with unprotected LMCA has, in fact, been completed. In the LE MANS trial (23), the investigators hypothesized that avoiding cardiopulmonary bypass for the preferential performance of PCI would result in improved convalescent left ventricular function, and, indeed, in this study, the resting LVEF rose from similar baseline values to a higher level in the PCI group at 12 months (60.3 ± 12.6% vs. 54.0 ± 9.1%, p = 0.037). With follow-up completed at a mean duration of 40 months, the survival and angina status were similar in both groups, with no occurrences of stent thrombosis reported.

While these results are intriguing, a large, multicenter randomized trial of PCI versus CABG is required before serious consideration can be given to angioplasty supplementing surgery for LMCA disease. Such a study, the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus DES and cardiac surgery) trial, is nearing completion. In the SYNTAX trial, 1,800 patients with LMCA and/or 3-vessel disease (with a minimum of 710 patients with significant left main lesions) are being randomized to CABG versus PCI with paclitaxel-eluting stents (24). The primary end point is the 12-month composite occurrence of death, stroke, myocardial infarction, or repeat revascularization. The principal results of the SYNTAX trial are anticipated in the fall of 2008, and although concerns will be voiced regarding the limited duration of follow-up and constant evolution of drugs, devices, and techniques, it is likely that this study will establish the standard to guide revascularization decisions for patients with extensive coronary artery disease for the foreseeable future. Thus, despite the fact that LMCA stenting with DES is currently a viable treatment alternative in Europe (25), pending SYNTAX, the principles of evidence-based medicine would dictate that CABG remain the gold standard for most patients with unprotected LMCA disease who are good surgical candidates.

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