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EDITORIAL COMMENT

Proximal Left Anterior Descending Coronary Artery PCI

Is it No Longer the Last Lesion Standing?*

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Percutaneous coronary intervention in several lesion subsets historically has been deferred in favor of coronary artery bypass grafting (CABG) due to improved clinical outcomes with surgical revascularization. These have previously included lesions in the left main coronary artery, complex multivessel coronary artery disease, and proximal disease of the left anterior descending coronary artery (LAD). However, the interventional community has been diligently working to optimize the outcomes in these higher-risk lesion subsets with improved procedural techniques, stent technology, risk factor modification, and adjunctive medical therapy. A study by Roguin et al. (1) in this issue of *JACC: Cardiovascular Interventions* makes the case that the proximal LAD is no longer off-limits for percutaneous coronary intervention (PCI).

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Roguin et al. (1) report the 4-year outcomes of stenting of the proximal LAD in patients enrolled in the PROTECT trial (Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial), a randomized open-label study of patients assigned to treatment with the Endeavor zotarolimus-eluting stent (Medtronic, Santa Rosa, California) versus the Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson, Miami Lakes, Florida) from May 2007 through December 2008. This post hoc substudy evaluates the outcomes to 4 years of patients treated that included a lesion in the proximal LAD (n = 2,534, 29.1% patients) versus those whose revascularization did not include the proximal LAD (n = 6,172, 70.9% patients). The 4-year mortality rates were equivalent in the 2 groups at 5.8%, but a higher rate of myocardial infarction (MI) was seen in the proximal LAD group compared with those without proximal LAD revascularization (6.2% vs. 4.9%; p = 0.015). Target vessel failure (TVF) (defined as cardiac death, target vessel MI, or clinically driven target vessel revascularization [TVR] by percutaneous or surgical methods) and major adverse cardiac events (MACE) (defined as all-cause death, MI, emergent CABG, or repeat clinically indicated target lesion percutaneous or surgical revascularization) did not differ between groups, with rates of each in the range of 13.5% to 15%. Stent thrombosis was seen in 2% of patients in each group. Multivariate analysis demonstrated proximal LAD stenting as a significant predictor of MI, but not TVF or MACE.

The majority of available data on clinical outcomes in isolated proximal LAD revascularization come from studies comparing PCI with CABG, predominantly in the bare-metal stent era. Two meta-analyses of these trials demonstrated similar mortality and myocardial infarction rates, but significantly lower revascularization rates and recurrence of angina with minimally invasive left internal mammary artery (LIMA) (2,3). A more recent study from the New York State PCI reporting system described the outcomes of a propensity-matched analysis of CABG versus drug-eluting stenting for isolated proximal LAD revascularization (4). Three-year mortality rates did not differ, nor did the combined endpoint of death, MI, or stroke; however, repeat revascularization was approximately 50% less with CABG. Given the years of study enrollment, this included first-generation drug-eluting stents, and the revascularization rates were not further differentiated.

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There are a number of concerns about this study that need to be acknowledged. First, the study was a non-pre-specified post hoc analysis and therefore subject to unaccounted-for confounders. Second, when placing the results of the study by Roguin et al. (1) in the context of patient care, it is important to note the very different patient profile in the proximal LAD versus nonproximal LAD cohorts. Although the proximal LAD lesion site is known to be a higher-risk location, the demographic characteristics of this patient subgroup represent lower risk (younger, less smoking, less hypertension, less hyperlipidemia, fewer prior CABG or PCI). This suggests a possible selection bias for inclusion in this PCI trial, likely instead of referral for surgical revascularization. However, there was a higher-risk angiographic profile in the proximal LAD cohort, with significantly more bifurcation lesions, greater number of lesions treated and stents per patient, and a greater total stent length per patient. This likely resulted in the significantly higher rate of continued dual-antiplatelet therapy in the proximal LAD cohort at 4 years. Thus, the evaluation of such outcome data must include the assumption of pre-selection of certain patient and lesion characteristics as likely occurred in this study.

Third, the adverse outcomes reported in this study require further evaluation. It is notable that rates of MI are significantly higher in the proximal LAD group compared with the outside of the proximal LAD group; and these significant differences are sustained from 6 months to 4 years. With target lesion failure (TLF) and TVF both significantly higher at 1-, 2-, and 3-year follow-up in the proximal LAD group, only TLF remains significantly higher at 4 years. However, numerically, each endpoint regarding revascularization is higher in the proximal LAD group. So which endpoint is the most important in a study such as this? An interventional viewpoint would state that despite the higher rate of MI and TLF in the proximal LAD location, this was not associated with higher mortality. The surgical point of view would note that MI and TLF are consistently higher in the proximal LAD group. Additional benefit regarding protection of events within the target vessel with a LIMA to reduce TVR would also favor surgery. One also can question what is the appropriate time frame to follow up in a PCI trial. We have learned that longer-term follow-up in PCI versus CABG trials may be necessary to see a survival advantage of CABG, but such a signal of mortality difference in this PCI trial is not seen here out to 4 years.

Fourth, although this is a clinical trial comparing PCI alone between proximal LAD lesions and LAD lesions outside of the proximal segment, it is important to compare these results to reported data with LIMA grafting for proximal LAD disease. In the meta-analysis of Kapoor et al. (5), the 5-year repeat revascularization rate of a LIMA for isolated proximal LAD disease was 7.3% at 5 years, whereas in the current study at 4 years, the TVF rate was double that at 13.5% to 14.8%. This represents a significant improvement over rates reported with bare-metal stents, however, still twice as high as those seen with a LIMA. An additional challenge in many stent trials such as this one is that the technology may have advanced beyond that evaluated by the time the results are published. This represents such an example in that the 3 stents evaluated are first generation, and no longer commercially available drug-eluting stents. Given the improvement in terms of optimizing safety and efficacy with third-generation drug-eluting stents, it is likely that this study with current technology would show reduction, not only in repeat revascularization events, but also in stent thrombosis.

The current focus on PCI versus CABG for complex lesions such as the left main coronary artery has been of great interest with the publication of the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trials. The EXCEL trial randomized 2,900 patients to PCI with a Xience drug-eluting stent of the left main versus CABG in patients with a SYNTAX score <32 (6). Although there was an early hazard of increased events in the CABG group primarily driven by increased MI; at 3 years, there was no significant difference in the primary endpoint of death, stroke or MI. However, a trend toward increased mortality in the PCI arm may be significant at 5 years. The NOBLE trial randomized 1,201 patients with left main disease and no more than 3 additional lesions but in all ranges of SYNTAX score to PCI versus CABG (7). The primary endpoints of major adverse cardiovascular and cerebrovascular events (MACCE) included death, nonprocedural MI, repeat revascularization, and stroke. At a 5-year follow-up, there was a significantly higher rate of MACCE in the PCI arm irrespective of SYNTAX score, primarily driven by MI and repeat revascularization. This current paper shows many parallel results with these publications while also focusing on a high-risk lesion subset that has historically lead to referral for surgical revascularization. The current study shows similar findings with long-term follow-up to 4 years demonstrating no mortality difference in proximal LAD PCI versus

nonproximal LAD PCI, however at the cost of higher rates of MI and TLR.

Over the past decade, as we evaluated lesion subsets previously referred for coronary artery bypass surgery, we have learned that shorter-term follow-up may demonstrate no difference in mortality, but that longer-term follow-up of at least 5 years is likely necessary to demonstrate such differences. The risk of higher MI and higher repeat revascularization with PCI is part of the equation to consider. Given that a randomized trial of PCI versus CABG for proximal LAD lesions is unlikely to occur, is this trial enough to move the needle a little more away from surgery or is the proximal LAD still one of the last lesions standing? The answer may be that it depends on which outcomes are considered most important to the patient and the physician.

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REFERENCES

1. Roguin A, Camenzind E, Kerner A, et al. Long-term outcomes of stenting the proximal left anterior descending artery in the PROTECT trial. J Am Coll Cardiol Intv 2017;10:548–56.

2. Jaffery Z, Kowalski M, Weaver WD, Khanal S. A meta-analysis of randomized control trials comparing minimally invasive direct coronary bypass grafting versus percutaneous coronary intervention for stenosis of the proximal left anterior descending artery. Eur J Cardiothorac Surg 2007;31:691–7.

3. Aziz O, Rao C, Panesar SS, et al. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. BMJ 2007;334:617.

4. Hannan EL, Zhong Y, Walford G, et al. Coronary artery bypass graft surgery versus drug-eluting stents for patients with isolated proximal left anterior descending disease. J Am Coll Cardiol 2014;64:2717–26.

5. Kapoor JR, Gienger AL, Ardehali R, et al. Isolated disease of the proximal left anterior descending artery comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. J Am Coll Cardiol Intv 2008;1:483–91.

6. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223–35.

7. Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743–52.

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