JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 23, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jcin.2017.09.038

EDITORIAL COMMENT

Left Main Disease

At the Intersection of Surgery and Stents*

David E. Kandzari, MD,[a] Jeffrey W. Moses, MD[b]

In a lesion subset once routinely excluded from interventional cardiology trials, a succession of studies comparing drug-eluting stents (DES) and coronary artery bypass surgery for the treatment of unprotected left main coronary artery disease have supported a reappraisal of established conventions and broadened therapeutic options. Although varied in trial design, methods, and study population size, these trials consistently demonstrated clinical equipoise between revascularization strategies regarding safety outcomes of death, myocardial infarction, and stroke but also, in selected instances, suggested more apparent benefit to support (or dismiss) one method over another (1,2).

Unlike many promising therapies in cardiovascular medicine, in the case of left main percutaneous revascularization, enthusiasm for a less invasive alternative treatment for complex coronary disease did not outpace the evidence. Instead, the adoption of unprotected left main percutaneous coronary intervention (PCI) has represented a graduated evolution of studies in technique, advances in technology, and performance of trials that inform clinical, health status, and economic outcomes. Early discouraging reports with balloon angioplasty or bare-metal stents were confounded by patients selected for high risk, compassionate use, and/or nascent procedural technique, contributing to at best, inconsistent intermediate-term clinical outcomes and at worst, unacceptably high rates of restenosis-related complications manifest as repeat revascularization, myocardial infarction, or even sudden cardiac death. In following decades, societal guidelines also remained reticent to endorse unprotected left main PCI only but in patients considered ineligible for surgery.

With supportive data from more contemporary trials and modest advancements in international guidelines to advocate unprotected left main PCI in settings of excess surgical risk and/or limited disease complexity, performance of left main PCI did begin to advance in selected geographies. However, what has been, until recently, largely unaddressed is the much broader patient population with low to intermediate disease complexity for whom both surgical and percutaneous revascularization may be considered. To this purpose, the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial represented an international, randomized study designed by a heart team of surgeons, interventionalists, and noninvasive practitioners with the intent of applying best practices in technique, technology, and medical care (3). Among 1,905 randomized patients, the study demonstrated statistical and clinical parity regarding the 3-year composite outcome of death, myocardial infarction, and stroke. Repeat revascularization was more common among PCI patients, whereas symptomatic graft occlusion and stent thrombosis were more frequent in the surgery cohort. Although the timing of selected events (e.g., myocardial infarction) differed between revascularization strategies, both procedure-related and spontaneous events conveyed prognostic relevance.

Against this background of supportive clinical trials evidence, unprotected left main PCI has gradually become integrated into routine practice, in many instances representing patients whose clinical characteristics and outcomes are underreported in clinical

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [a]Piedmont Heart Institute, Atlanta, Georgia; and the [b]Columbia University Medical Center, New York, New York. Dr. Kandzari has received institutional research and grant support from Abbott, St. Jude, Biotronik, Boston Scientific, Medinol, Medtronic, and Orbus Neich; and personal consulting honoraria from Biotronik, Boston Scientific, Medtronic, and Micell Technologies. Dr. Moses has reported that he has no relationships relevant to the contents of this paper to disclose.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 23, 2017
DECEMBER 11, 2017:2411–3

trials. Although approximately 60% of patients included in the EXCEL screening registry might be considered candidates for PCI based on the randomized trial results (3), still a meaningful group of patients who do not fulfill trial criteria are treated in everyday practice. Surveys inclusive of "real world" practice are important because even trials randomizing "all comers" without restriction enroll lower risk populations than patients not randomized but instead followed in a registry. With advancing interest in left main PCI, observational studies inclusive of broader, less selected patient populations reflect clinical decision making, evolution of PCI technique, and, in some measure, external validation of outcomes observed in more dedicated trials. Perspectives from clinical experience complement issues unaddressed in more formal trials limited by conservative enrollment criteria, prescriptive patient selection, and standardized procedural technique. Although comparisons of results across trial designs are challenged by substantial differences in endpoint definitions, ascertainment, and patient selection, the insight to current practice from large registry studies is unequaled.

SEE PAGE 2401

Along the storied path of left main clinical studies, the DELTA (Drug Eluting Stent for Left Main Coronary Artery) registry database represents 1 of the largest surveys of left main PCI in clinical practice and has served a formative role in our understanding of this treatment strategy as it has developed over time. Initially reporting procedural and clinical outcomes among 2,775 (nonrandomized) patients with left main disease treated with either PCI using first-generation DES or bypass surgery, the DELTA 1 investigators reported over 3.5-year follow-up a similar occurrence of death, myocardial infarction, and stroke between revascularization strategies yet a higher incidence of repeat target vessel revascularization with PCI Chieffo et al. (4). In this issue of *JACC: Cardiovascular Interventions*, early procedural and intermediate-term outcomes are now presented from the DELTA 2 registry (5), an observational study of left main PCI using more contemporary DES and with comparison with the prior DELTA 1 cohort of bypass surgery patients. Despite its observational design, the analysis is important as it represents 1 of the largest collective multicenter experiences of left main PCI performed at institutions with skilled operators who have adopted this treatment strategy in routine clinical practice. Second, the study reflects a broad representation of patients with considerable variance in clinical and lesion complexity, many of whom would be systematically excluded from participation in clinical trials.

Despite differences in enrollment criteria and the absence of more uniform, protocol-mandated treatment and follow-up, it is notable that the outcomes observed in the DELTA 2 registry share similar themes with those from contemporary randomized trials. First, the study demonstrates a comparable (in this case significantly lower) rate of the composite endpoint of death, myocardial infarction, and stroke among PCI patients compared with a matched cohort of patients undergoing surgery (10.3% vs. 11.6%; adjusted hazard ratio: 0.73; 95% confidence interval: 0.55 to 0.98; $p = 0.03$). Alternatively, although treatment with newer generation DES is associated with improved efficacy compared with predicate designs, repeat revascularization remains more common than with bypass surgery (1,3). Furthermore, risk for stroke is higher among surgery patients, a consistent finding among earlier but not current randomized comparisons with bypass surgery (3,6). Although this latter observation may reflect the use of a more dated surgical experience as a comparator group in the present study, it is notable that the stroke event rate in the DELTA 1 and EXCEL bypass surgery cohorts was similar over a comparable follow-up period.

Like any observational study, conclusions from the registry are limited by the nonrandomized design of the study and the influence of unmeasured variables on treatment decisions and outcomes. Although the absence of pre-specified enrollment criteria broadens the generalizability to routine clinical practice, the lack of insight to decision making for revascularization strategy and uncertainties regarding consecutive enrollment limit insight to patient selection. Limited follow-up duration and potential for underreporting of events also challenge estimates. For example, although the rate of cardiac death in the DELTA 2 registry is expectedly higher compared with more conservative, randomized clinical trials, myocardial infarction and stroke are lower than what might be anticipated in a less selective, more complex patient population. As the analysis describes results relative to a less contemporaneous surgery cohort, what is also of interest is whether PCI procedural technique and outcomes have advanced over a more than 10-year experience within the combined DELTA registries, as has been demonstrated in other series evaluating temporal patterns of left main percutaneous revascularization (7).

With supportive data from a large, randomized clinical trial and complementary evidence from a broad clinical experience, what more is needed before

adopting unprotected left main PCI in practice? Although not entirely consistent with the EXCEL trial criteria, revised appropriate use criteria are now more inclusive of conditions that support left main PCI. Alternatively, a separate randomized trial with different methods and endpoints, the NOBLE study, did not demonstrate noninferiority of PCI and bypass surgery for left main disease (8). Furthermore, late-term follow-up of EXCEL and NOBLE is of interest, although to date, reported rates of cardiovascular death and events specifically related to the left main territory are nearly identical, if not favor PCI. Optimization of technique related to stenting methods (NCT02497014), intravascular imaging, hemodynamic support, and even vascular access is also a focus of ongoing study. Refinement of risk models may further inform patient selection and consent. Finally, forthcoming comparative assessment of health status and economic outcomes between revascularization strategies is awaited. Indeed, previous study from comparative left main trials, including the DELTA registry, suggests that the 2 treatment strategies may be even more equivalent from a patient perspective when recovery and both short- and late-term adverse events are weighted (9).

Still, resolution of such outstanding uncertainties will only refine left main PCI procedural and clinical outcomes, but they do not present a barrier to offering PCI for responsibly selected patients as an alternative to bypass surgery in today's practice. At least among experienced centers, left main PCI is offered for selected patients with clinical and anatomic features representative of the EXCEL trial and following heart team consensus; for others, pending experience with procedural technique and consensus between cardiology and surgical societies, left main PCI will more commonly remain reserved for patients considered unsuitable for bypass surgery.

ADDRESS FOR CORRESPONDENCE: Dr. David E. Kandzari, Piedmont Heart Institute, 95 Collier Road, Suite 2065, Atlanta, Georgia 30309. E-mail: david.kandzari@piedmont.org.

REFERENCES

1. Nerlekar N, Ha FJ, Verma KP, et al. Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis: a meta-analysis of randomized trials. Circ Cardiovasc Interv 2016;9:e004729.

2. Cavalcante R, Sotomi Y, Lee CW, et al. Outcomes after percutaneous coronary intervention or bypass surgery in patients with unprotected left main disease. J Am Coll Cardiol 2016;68:999–1009.

3. 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.

4. Chieffo A, Meliga E, Latib A, et al. Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. J Am Coll Cardiol Intv 2012;5:718–27.

5. Chieffo A, Tanaka A, Giustino G, et al. The DELTA 2 registry: a multicenter registry evaluating percutaneous coronary intervention with new-generation drug-eluting stents in patients with obstructive left main coronary artery disease. J Am Coll Cardiol Intv 2017;10:2401–10.

6. Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery trial. Circulation 2014;129:2388–94.

7. Park SJ, Ahn JM, Kim YH, et al. Temporal trends in revascularization strategy and outcomes in left main coronary artery stenosis. Data from the Asan Medical Center-Left Main Revascularization registry. Circ Cardiovasc Interv 2015;8:e001846.

8. 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.

9. Capodanno D, Gargiulo G, Buccheri S, et al. Computing methods for composite clinical endpoints in unprotected left main coronary artery revascularization: a post hoc analysis of the DELTA registry. J Am Coll Cardiol Intv 2016;9:2280–8.

KEY WORDS left main, percutaneous coronary intervention, registries