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EDITORIAL COMMENT

Coronary Bypass Surgery Versus Percutaneous Coronary Intervention in Left Main and Multivessel Disease

Incremental Data—How Do We Apply It?*

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Is coronary artery bypass grafting (CABG) superior to percutaneous coronary intervention (PCI) for revascularization for left main and multivessel coronary disease?

The development and refinement of coronary stents created the possibility that stents could achieve coronary revascularization as effectively and durably as CABG. However, group data from randomized trials have shown consistently that CABG confers a modest long-term survival superiority compared with PCI, particularly for certain patient subsets (such as patients with diabetes mellitus) and a substantially decreased requirement for repeat revascularization (1-6).

The substantially more noxious experience for the patient undergoing CABG as compared with PCI drives an ongoing search to define a role for PCI in the left main and multivessel disease patient populations. This search seeks to identify patient characteristics for which PCI is either equivalent or, potentially, the preferred revascularization modality. The 2011 American College of Cardiology/American Heart Association/Society For Cardiovascular Angiography and Interventions Guidelines for Percutaneous Coronary Intervention (7) and the 2014 European Society of Cardiology Guidelines on Myocardial Revascularization (8) endorse PCI as an alternative to CABG in multivessel or left main coronary disease for selected patients with numerous qualifications and caveats.

Despite 25 years of randomized trial clinical research, the PCI versus CABG choice remains a complex clinical judgment challenge that should be informed by outcomes data. It is challenging to study with randomized trials due to the number and complexity of variables that affect outcomes, as well as the relatively small effect sizes, which require large datasets to generate sufficient statistical power for meaningful analysis (particularly of subgroups). The effort required to enroll subjects is substantial. Thus, although any successfully completed large trial deserves great respect, there is a continual desire for larger study populations to permit greater statistical power for analysis.

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The study reported in this issue of *JACC: Cardiovascular Interventions* by Lee et al. (9) provides incremental information to guide case selection between PCI and coronary bypass surgery. They combined data from 3 contemporary randomized trials that used similar patient populations, study designs, and data elements—SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) (10), BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease) (4) and PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) (5)—to assemble a large (n = 3,280) patient population

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randomized between PCI or CABG. The methodology permitted incorporating the primary data from the 3 individual trials into a single data set enabling a patient-level rather than a trial-level meta-analysis. Accordingly, in addition to its primary outcome finding, its statistical power provides one of the best estimates available for overall group outcomes and permits some subgroup exploration.

Consistent with earlier studies, they found primary endpoint (combined all cause death, myocardial infarction and stroke) superiority for CABG over PCI at the 5-year follow-up (CABG: 13%; PCI: 16%; $p = 0.046$). Of particular interest, the primary outcome event rate was mainly driven by a greater frequency of late myocardial infarction in the PCI group, which was statistically significant on its own (CABG: 3.1%; PCI: 6.7%; $p = 0.001$). The point estimates for death from any cause (CABG: 8.7%; PCI: 10.3%; $p = 0.20$) and death from cardiac causes (CABG: 4.9%; PCI: 6.5%; $p = 0.07$) trended in favor of CABG.

Although the study's finding of CABG superiority for the overall population is striking, does it mean that that CABG is overall superior to PCI in the entire multivessel and left main population? Or, within this population, are there cohorts for whom PCI is either equivalent or potentially superior to CABG? This is the core question for clinicians seeking to make an optimal recommendation to a particular patient. Does this study provide insight into subgroup outcomes, which can be applied to guide case selection for PCI versus CABG within this large, heterogeneous population?

This study population's characteristics are skewed somewhat toward higher risk for PCI (27% had a SYNTAX score ≥33) and toward lower risk for CABG (82% had a EuroSCORE [European System for Cardiac Operative Risk Evaluation] <6); both group characteristics that would favor CABG over PCI. Major subgroup analysis confirmed the previously demonstrated progressive advantage of CABG over PCI with increasing anatomic SYNTAX score. In particular, (as was found in the SYNTAX trial) CABG and PCI outcomes were equivalent in subjects with anatomic SYNTAX scores <22.

Two important subgroup findings are that CABG performed better than PCI for patients with multivessel disease without left main involvement (CABG: 11.6%; PCI: 17.3%; $p = 0.001$), but not for patients with left main disease (CABG: 15.1%; PCI: 14.7%; $p = 0.46$). As was the case with late myocardial infarction, both outcome differences emerged at 6 months post-procedure and continued to widen progressively. This suggests that stent thrombosis, restenosis, and, possibly, untreated lesion progression may have been important contributors to the difference between the left main and multivessel disease cohort. The recently reported EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (11) and LeftMain NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) (12) trials (both of left main disease) found similarly greater trends in their PCI cohorts toward late-occurring myocardial infarction and death.

The better outcomes demonstrated for CABG in the multivessel disease cohort, particularly in the cohort with high SYNTAX scores, is thought provoking and may have implications for case selection in this population. The left main cohort may have been less technically challenging anatomically to treat with PCI than the multivessel cohort. This suggests that patients who require multilesion treatment and who are challenging to treat anatomically by PCI are more likely to achieve a successful and durable revascularization by CABG. Consequently, they may enjoy a better outcome if treated surgically. The ongoing greater frequency of myocardial infarction over the 5-year follow-up emphasizes the greater vulnerability of PCI patients to late adverse events, particularly to the increased risk of restenosis and late stent thrombosis as the number and complexity of treated sites increases.

It is also noteworthy that CABG and PCI event rates were similar in diabetics and nondiabetics. This finding is unexplained and is inconsistent with multiple earlier trials (including SYNTAX, whose data are included in this study cohort) (10,13) and the large FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), which included 1900 patients with diabetes with increased all-cause 5-year mortality in the PCI group (PCI: 16.3%; CABG, 10.9%; $p = 0.046$) (3). This disparity in results between the current study and earlier trials in diabetic patients requires further clarification.

This study is complementary to an analysis recently published in *JACC: Cardiovascular Interventions* by Sotomi et al. (14), in which the SYNTAX Score II was applied to the combined BEST and PRECOMBAT datasets. The SYNTAX Score II, which was developed from the SYNTAX dataset, predicts mortality only as an endpoint (does not include myocardial infarction and stroke) and has separate prediction algorithms for PCI and CABG. It is noteworthy that the SYNTAX Score II algorithms for PCI and CABG incorporate very different variables. Based on SYNTAX Score II risk

prediction for both PCI and CABG, the Sotomi et al. (14) study identified 3 patient cohorts: PCI preferred, CABG preferred, and equipoise. It found poorer outcomes in patients assigned to the not-preferred therapy. The Lee et al. (9) study is congruent with the Sotomi et al. study, demonstrating superior performance of CABG in advanced anatomic disease, which would be more likely to score as CABG preferred with the SYNTAX Score II algorithm.

It is possible that the PCI performance represented in this trial is not optimal state of the art and that PCI outcomes could be improved by more refined lesion selection. The FAME 2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial (15) demonstrated convincingly that, for PCI, it is detrimental to treat stenoses that are not important functionally. Thus, it is possible that in the SYNTAX, BEST, and PRECOMBAT trials, the performance of PCI was degraded because some lesions were treated that would be better left alone. The FAME 3 trial (16), currently in progress, will compare PCI with stenosis severity confirmed by fractional flow reserve to CABG. Potentially, if fractional flow reserve guidance improves the performance of PCI, the equipoise range of the 2 techniques may expand, making PCI an appropriate treatment for a larger fraction of left main and multivessel disease patients.

Clinicians confronting revascularization modality choices between PCI and CABG for patients with left main and multivessel coronary disease are responsible to make careful case selection choices informed by outcomes data. The Lee et al. study and other comparisons of PCI to CABG for left main and multivessel coronary disease are expanding progressively the understanding of the relative roles for PCI and CABG in this large, complex, and heterogeneous patient population. We can apply these findings to increase the sophistication and accuracy with which we identify the optimal treatment strategy for individual patients.

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REFERENCES

1. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.

2. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.

3. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.

4. Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015;372:1204–12.

5. Ahn JM, Roh JH, Kim YH, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. J Am Coll Cardiol 2015;65:2198–206.

6. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.

7. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society For Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.

8. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

9. Lee CW, Ahn J-M, Cavalcante R, et al. Coronary artery bypass surgery versus drug-eluting stent implantation for left main or multivessel coronary artery disease: a meta-analysis of individual patient data. J Am Coll Cardiol Intv 2016;9:2481–9.

10. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

11. 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 Oct 31 [E-pub ahead of print].

12. Mäkikallio 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 Oct 31 [E-pub ahead of print].

13. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432–40.

14. Sotomi Y, Cavalcante R, van Klaveren D, et al. Individual long-term mortality prediction following either coronary stenting or bypass surgery in patients with multivessel and/or unprotected left main disease: an external validation of the SYNTAX score II model in the 1,480 patients of the BEST and PRECOMBAT randomized controlled trials. J Am Coll Cardiol Intv 2016;9:1564–72.

15. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208–17.

16. Zimmermann FM, De Bruyne B, Pijls NH, et al. Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial: a comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease. Am Heart J 2015;170:619–26.e2.

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