

EDITORIAL

# Treatment of Left Main Disease: Let the Patient Choose

Itzik Ben-Dor, MD; Ron Waksman , MD

The choice between percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) for the treatment of left main coronary artery (LMCA) disease has been debated for over a decade. When tackling the controversy, we need to take into account the heterogeneity of the disease, that is, location (ostial, body, or bifurcation), with or without involvement of the coronary tree, with or without diabetes mellitus, young versus elderly, and men versus women. Further, the lack of uniformity of end points across trials makes it difficult to pool studies together for meta-analyses. The 2 largest published randomized trials with 5-year follow-up data showed conflicting results. The EXCEL<sup>1</sup> (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (N=1905) demonstrated that at 5 years, both PCI and CABG had similar incidence of the primary composite end point (all-cause death, myocardial infarction [MI], and stroke). In contrast, the NOBLE (Nordic–Baltic–British Left Main Revascularisation) trial<sup>2</sup> (N=1201) demonstrated superiority of CABG over PCI for the primary composite end point of all-cause death, non-procedural MI, repeated revascularization, and stroke at 5 years. These results are mainly driven by the differences in MI and repeat revascularization rates in both groups. Importantly, all-cause mortality was higher in the PCI group versus the CABG group in the EXCEL trial (odds ratio [OR], 1.38; 95% CI, 1.03–1.85), with no differences noted in cardiovascular mortality (OR, 1.26; 95% CI, 0.85–1.85).

---

**See Article by Jeong et al.**

---

Adding to this, 3 recent meta-analyses also demonstrated conflicting results. In the meta-analysis of 5 randomized trials (4612 patients) done by Ahmad et al, both PCI and CABG showed no differences in mortality and clinical events at 10-year follow-up.<sup>3</sup> Zhang et al<sup>4</sup> performed a meta-analysis of 4 randomized trials including 4394 patients and showed that there are no significant differences in all-cause mortality, stroke, or MI in patients with a low or intermediate SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) score (hazard ratio [HR], 1.20; 95% CI, 0.85–1.70), but there was a higher incidence following PCI in patients with a higher SYNTAX score (HR, 1.64; 95% CI, 1.20–2.24). In the largest meta-analysis, of 23 clinical trials and retrospective studies (13 260 patients),<sup>5</sup> the PCI arm was noted to have significantly higher cardiovascular mortality (incidence ratio, 1.24; 95% CI, 1.05–1.45) and noncardiovascular mortality (incidence ratio, 1.19; 95% CI, 1.00–1.41) relative to CABG. However, a major criticism of this meta-analysis is the heterogeneity of the patient population, with varying clinical presentation limiting broad conclusions about treatment effect.

In response to the results from the clinical trials and the meta-analyses, the 2018 European clinical practice guidelines for myocardial revascularization supported PCI of the LMCA, with a Class I recommendation and level of evidence A if the SYNTAX

**Key Words:** Editorials ■ coronary artery bypass graft surgery ■ left main coronary artery disease ■ mortality ■ outcome ■ percutaneous coronary intervention

---

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Ron Waksman, MD, FACC, MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, 110 Irving St., NW, Suite 4B-1, Washington, DC 20010. E-mail: ron.waksman@medstar.net

For Disclosures, see page 3.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

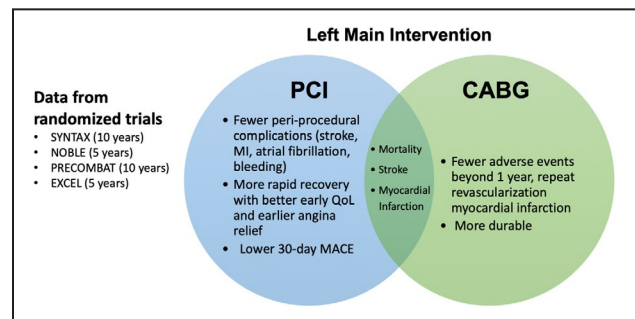
score was <22, and Class IIa recommendation with level of evidence A if the SYNTAX score was 23 to 32.<sup>6</sup> In contrast, the American Heart Association/American College of Cardiology guidelines vary in their recommendations for PCI depending on the location of the disease in the LMCA. PCI for ostial or shaft LMCA disease has a Class IIa recommendation, whereas distal LMCA disease has a Class IIb recommendation (Level of Evidence: B, for both).<sup>7</sup> The outcomes of nondistal lesions treated with PCI are favorable.<sup>8,9</sup>

Currently, no specific recommendation exists concerning the optimal revascularization strategy in patients with diabetes mellitus and isolated left main disease.

The PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial was a randomized trial of patients with LMCA disease comparing PCI with sirolimus-eluting stents (n=300) or CABG (n=300). In the study in this issue of the *Journal of the American Heart Association (JAHA)*, Jeong et al<sup>10</sup> reported extended follow-up (10 years) focusing on the outcome of patients with or without diabetes mellitus. The 10-year rates of major adverse cardiac or cerebrovascular events, death, MI, stroke, and its composite outcomes were not significantly different after PCI or CABG in patients with and without diabetes mellitus, but the risk of target vessel revascularization and repeat revascularization was consistently higher after PCI, irrespective of diabetes mellitus. The authors conclude that the presence of diabetes mellitus should not sway us in choosing the specific revascularization strategy for left main disease. However, the study findings should be interpreted with caution. Although it is a randomized study with long-term follow-up, the study is underpowered to provide a definite answer for the best treatment strategy for left main intervention in patients with diabetes mellitus. In this study, major adverse cardiac or cerebrovascular events were higher in the PCI group versus the CABG group in patients with diabetes mellitus (36.3% versus 26.7%; HR, 1.35; 95% CI, 0.83–2.19,  $P=0.23$ ). In patients without diabetes mellitus, this difference is smaller (25.3% versus 22.9%, respectively; HR, 1.15; 95% CI, 0.79–1.67,  $P=0.48$ ). Other limitations of this study include the use of first-generation drug-eluting stents; second-generation drug-eluting stents and optimization of PCI technique might improve the PCI outcome. Because of the small number of patients, the PRECOMBAT trial did not have sufficient power to detect statistically significant differences in clinical end points in each subgroup according to diabetes mellitus status. In the diabetic group, the number of patients treated with insulin was only 10%. Patients

who are insulin dependent might have worse outcomes, as shown by Bawamia et al,<sup>11</sup> where the impact of diabetes mellitus on mortality outcomes following left main PCI was significant only in the patients treated with insulin.

The current study findings are also consistent with prior results from the EXCEL study<sup>12</sup> and a pooled analysis of individual randomized patient data<sup>13</sup> from the SYNTAX, PRECOMBAT, EXCEL, and NOBLE trials (Figure). In all these studies, there was no significant difference in 3- or 5-year mortality after treatment of patients with LMCA disease with PCI versus CABG in patients with or without diabetes mellitus. However, in the pooled analysis, CABG showed a superior survival rate when compared with PCI in patients with diabetes mellitus and multivessel disease but without LMCA involvement. Wang et al<sup>14</sup> reported data from 8 studies (3 randomized trials and 5 observational studies) with a total of 3835 patients with diabetes mellitus and showed that all-cause mortality (risk ratio [RR], 0.85; 95% CI, 0.73–1.00;  $P=0.05$ ), MI (RR, 0.53; 95% CI, 0.35–0.80;  $P=0.002$ ), repeat revascularization (RR, 0.34; 95% CI, 0.26–0.46;  $P=0.00001$ ), and target vessel revascularization (RR, 0.26; 95% CI, 0.18–0.38;  $P=0.00001$ ) were significantly lower with CABG when compared with PCI in patients with diabetes mellitus and left main disease. This study also showed that CABG was associated with a significantly higher risk of stroke (RR, 2.16; 95% CI, 1.39–3.37;  $P=0.0007$ ). The MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical



**Figure. Comparison between left main stem revascularization techniques for different outcomes according to the trials and their meta-analyses.**

CABG indicates coronary artery bypass graft surgery; EXCEL, Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; MACE, major adverse cardiac events; MI, myocardial infarction; NOBLE, Nordic-Baltic-British Left Main Revascularisation; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; QoL, quality of life; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

Revascularization) investigators<sup>15</sup> explored the interaction between diabetes mellitus and the revascularization method over the 10 years of follow-up. There was no significant difference in mortality or major adverse cardiac or cerebrovascular events between PCI and CABG in both patients with and without diabetes mellitus. Repeat procedures were lower with CABG than with PCI for both cohorts with and without diabetes mellitus.

In summary, heterogeneity of definitions of the primary composite end points and other confounders makes it impossible to draw a definitive conclusion for the optimal therapy for left main disease.

CABG and PCI for the treatment of LMCA disease should not be considered competitive but rather should be evaluated as alternative strategies chosen on the basis of patient characteristics, anatomic consideration, clinical presentation, and patient preference. Decision sharing with patients should include a discussion of the tradeoff of immediate better quality of life versus higher rate for repeat revascularization with PCI. Elderly patients (>75 years of age) have worse postoperative outcomes, including higher complications and mortality, and will probably choose PCI to shorten their recovery and morbidity at the price of higher risk for reintervention in the next 5 to 10 years. Meanwhile, young people may want to invest upfront and choose CABG knowing the durability of internal mammary artery patency. In some patients, however, especially those with diabetes mellitus, bilateral mammary cannot be used because of the risk of sternal wound infection, and this might change the equation to favor PCI. The investigators should be praised for extending the follow-up to 10 years, but interestingly, the long follow-up did not make much difference in patients' outcomes when comparing CABG versus PCI although we expect more graft failure at later time points and progression of disease in the stented coronary arteries.

CABG remains the standard of care for patients with diabetes mellitus, complex coronary artery disease, and multivessel coronary disease, as shown in the FREEDOM ((Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial; however, in this trial first-generation sirolimus-eluting and paclitaxel-eluting stents were used.<sup>16</sup> This does not apply automatically to patients with isolated left main disease. Left main lesions by nature are short but can be associated with complex bifurcation anatomy. Over the years, PCI has improved significantly, with new generations of drug-eluting stents that have thinner struts, durable and biodegradable polymers, and optimization of PCI techniques with intravascular imaging, new plaque modification techniques, and optimal pharmacological treatment; these iterations continued to narrow the gap when comparing outcome of CABG versus

PCI for left main disease. Further, diabetes mellitus is a heterogenous disease, that is, insulin- versus non-insulin-dependent, controlled versus uncontrolled, and new pharmacological therapeutics that can improve outcome. Therefore, diabetes mellitus should not be a deciding factor for the best treatment option for left main disease.

We can conclude that following the recent publications of outcome data from large randomized clinical trials and meta-analyses, there is now evidence to demonstrate equipoise regarding death, stroke, and MI between PCI and CABG in patients with left main disease. There was an increase in spontaneous MI in patients who had PCI, which was balanced by an increase in periprocedural MI in patients who underwent CABG and consistent observations of increased repeat revascularization rates in patients who had PCI. While we continue to debate the optimal strategy for revascularization for left main disease, the number of patients undergoing PCI for LMCA disease is increasing and the number of patients undergoing CABG is plummeting. The medical community already made its choice with the plethora of existing data. It is common in editorials related to CABG versus PCI studies like PRECOMBAT to call for more studies with larger sample sizes to identify which strategy is better. But the question is, do we really need more studies as we continue to struggle with confounders like age, gender, type of diabetes mellitus, etc? It is time to move on and focus on improving medical treatment and control of diabetes mellitus, improving stent technology, and optimizing PCI, and leave the decision of CABG versus PCI for the treatment of LMCA disease to the informed patient. Let the patient decide.

## ARTICLE INFORMATION

### Affiliation

Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC.

### Disclosures

Waksman is on the advisory board for Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd. and reports consulting for Abbott Vascular, Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd., Transmural Systems; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance; Transmural Systems. Ben-Dor has no disclosures to report.

## REFERENCES

1. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, Kandzari DE, Karpaliotis D, Brown WM III, Lembo NJ, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820–1830. DOI: 10.1056/NEJMoa1909406.

2. Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, Trovik T, Kellerth T, Kalinauskas G, Mogensen LJH, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet*. 2020;395:191–199. DOI: 10.1016/S0140-6736(19)32972-1.
3. Ahmad Y, Howard JP, Arnold AD, Cook CM, Prasad M, Ali ZA, Parikh MA, Kosmidou I, Francis DP, Moses JW, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2020;41:3228–3235. DOI: 10.1093/eurheartj/ehaa135.
4. Zhang J, Jiang T, Hou Y, Chen F, Yang K, Sang W, Wu H, Ma Y, Xu F, Chen Y. Five-year outcomes comparing percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in patients with left main coronary artery disease: a systematic review and meta-analysis. *Atherosclerosis*. 2020;308:50–56. DOI: 10.1016/j.atherosclerosis.2020.06.024.
5. Gaudino M, Hameed I, Farkouh ME, Rahouma M, Naik A, Robinson NB, Ruan Y, Demetres M, Biondi-Zoccai G, Angiolillo DJ, et al. Overall and cause-specific mortality in randomized clinical trials comparing percutaneous interventions with coronary bypass surgery: a meta-analysis. *JAMA Intern Med*. 2020;180:1638–1646. DOI: 10.1001/jamainternmed.2020.4748.
6. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165. DOI: 10.1093/eurheartj/ehy394.
7. Patel MR, Calhoun JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, Smith PK. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:2212–2241. DOI: 10.1016/j.jacc.2017.02.001.
8. Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airoldi F, Sangiorgi G, et al. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation*. 2007;116:158–162. DOI: 10.1161/circulationaha.107.692178.
9. Hyun J, Kim JH, Jeong Y, Choe K, Lee J, Yang Y, Kim TO, Park H, Cho S-C, Ko E, et al. Long-term outcomes after PCI or CABG for left main coronary artery disease according to lesion location. *JACC Cardiovasc Interv*. 2020;13:2825–2836. DOI: 10.1016/j.jcin.2020.08.021.
10. Jeong YJ, Ahn J-M, Hyun J, Lee J, Kim JH, Yang Y, Choe K, Park H, Kang D-Y, Lee PH, et al. Ten-year outcomes after drug-eluting stents or bypass surgery for left main coronary disease in patients with and without diabetes mellitus: the PRECOMBAT extended follow-up study. *J Am Heart Assoc*. 2021;10:e019834. DOI: 10.1161/JAHA.120.019834.
11. Bawamia BR, Egred M, Jackson M, Purcell I, Austin D, Zaman AG. Percutaneous coronary intervention for left main stem disease: impact of diabetes mellitus on mortality. *Catheter Cardiovasc Interv*. 2020;96:E416–E422. DOI: 10.1002/ccd.28818.
12. Milojevic M, Serruys PW, Sabik JF III, Kandzari DE, Schampaert E, van Boven AJ, Horkay F, Ungi I, Mansour S, Banning AP, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. *J Am Coll Cardiol*. 2019;73:1616–1628. DOI: 10.1016/j.jacc.2019.01.037.
13. Head SJ, Milojevic M, Daemen J, Ahn J-M, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939–948. DOI: 10.1016/S0140-6736(18)30423-9.
14. Wang H, Wang H, Wei Y, Li X, Jhummun V, Ahmed MA. Ten-year outcomes of percutaneous coronary intervention versus coronary artery bypass grafting for patients with type 2 diabetes mellitus suffering from left main coronary disease: a meta-analysis. *Diabetes Ther*. 2021;12:1041–1054. DOI: 10.1007/s13300-021-01025-x.
15. Lee K, Ahn J-M, Yoon Y-H, Kang D-Y, Park S-Y, Ko E, Park H, Cho S-C, Park S, Kim TO, et al. Long-term (10-year) outcomes of stenting or bypass surgery for left main coronary artery disease in patients with and without diabetes mellitus. *J Am Heart Assoc*. 2020;9:e015372. DOI: 10.1161/JAHA.119.015372.
16. Farkouh ME, Domanski M, Dangas GD, Godoy LC, Mack MJ, Siami FS, Hamza TH, Shah B, Stefanini GG, Sidhu MS, et al. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM follow-on study. *J Am Coll Cardiol*. 2019;73:629–638. DOI: 10.1016/j.jacc.2018.11.001.