

Left Main Stenting in 2020

Integrating EXCEL 5-year data into clinical practice.

BY YOUSIF AHMAD, MD, WITH COMMENTARY FROM CHRISTOPHER COOK, MBBS, BSc

The optimal method of revascularization for patients with left main coronary artery disease has been controversial. Traditionally, surgery with coronary artery bypass grafting (CABG) has been deemed the gold standard therapy,¹ but percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) has emerged as a valid alternative for selected patients. Longer-term randomized data comparing outcomes between CABG and PCI for left main coronary artery disease have been relatively lacking. Recent randomized trials have compared CABG to PCI with use of DES, and in 2018, European guidelines were updated to recommend PCI as an appropriate alternative to CABG in left main coronary artery disease with low-to-intermediate anatomic complexity (class I recommendation for low SYNTAX scores and class IIa for intermediate SYNTAX scores; the recommendation was against PCI [class III] for high SYNTAX scores).² Surgical societies have recently withdrawn their support for this guideline over perceived controversies with regard to the EXCEL trial.³

Three large-scale trials (SYNTAX,⁴ NOBLE,⁵ and EXCEL⁶) now have published longer-term follow-up results, furnishing clinicians and patients with significantly more data than ever before to inform therapeutic decision-making.

WHAT DO THE LATEST TRIAL DATA SAY?

The 5-year results of the EXCEL trial were recently published.⁶ In the EXCEL trial, 1,905 patients with left main coronary artery disease were randomized to PCI with DES (using the everolimus-eluting Xience stent system, Abbott) or CABG. The primary outcome measure was a composite of all-cause death, stroke, and myocardial infarction. This composite measure occurred in 22% of patients who underwent PCI and 19.2% of patients who underwent CABG; the difference between the two therapies was not statistically significant ($P = .13$). All-

cause mortality was statistically significantly greater with PCI (13% vs 9.9% with CABG), but the trial was not powered for this endpoint. There were no significant differences in cardiac death or myocardial infarction between the two groups.

EXCEL is not the only trial in this sphere to have recently published long-term results. The 5-year outcomes from the NOBLE trial were also recently published.⁵ The NOBLE trial randomized 1,201 patients with left main disease to either PCI or CABG. Most patients in the PCI arm were treated with the umirolimus-eluting BioMatrix stent system (Biosensors International). The primary outcome measure of the NOBLE trial was a composite of all-cause mortality, nonprocedural myocardial infarction, repeat revascularization, and stroke. This composite measure occurred more frequently with PCI than CABG (28% vs 19%; hazard ratio [HR], 1.58; 95% confidence interval [CI], 1.24–2.01; $P = .0002$). All-cause mortality was the same in the two groups (9% in each arm; HR, 1.08; 95% CI, 0.74–1.59; $P = .68$). Similarly, there was no difference in cardiac death (4% in each arm; HR, 0.99; 95% CI, 0.57–1.73; $P = .99$).

Even longer-term data have recently become available from the SYNTAX trial,⁴ which reported all-cause mortality results at 10 years. In this study, 357 patients with left main coronary artery disease underwent PCI and 348 underwent CABG. The PCI arm underwent treatment with the paclitaxel-eluting Taxus stent system (Boston Scientific Corporation). There was no difference in all-cause mortality at 10 years between the PCI group and the CABG group (26% vs 28%), despite the use of the now-defunct Taxus stent in the PCI arm.

LONG-TERM RESULTS

It has been argued that CABG offers a more durable result for patients with left main disease than PCI and that the benefits of CABG will be seen when longer-

term follow-up results are available because the patients treated with PCI will continue to accrue events the longer they are followed. Therefore, the results of long-term follow-up that have recently become available take on even greater importance. The longest available follow-up is from the SYNTAX trial (10 years). Despite the use of an old and now obsolete stent system, there was no difference in death from all-causes in the two groups. It is important to note that no other outcome measures besides all-cause mortality was available in the 10-year SYNTAX publication. The 5-year SYNTAX results⁷ had also shown no difference in all-cause death, cardiac death, or myocardial infarction between the two groups; the rate of repeat revascularization was higher with PCI, whereas the rate of stroke was higher with CABG.

The interpretation of clinical trials comparing PCI with CABG is also dependent on the time at which endpoints are measured. Thirty-day, and even 12-month, event rates favor PCI over CABG due to an up-front hazard of clinical events with CABG. This is clearly seen in the EXCEL 5-year data, in which three distinct periods of risk are seen: an early period in which CABG leads to greater events (up to 30 days), an interval period up to 12 months in which events are equal between arms, and a later period between 12 months and 5 years in which there are more events in the PCI arm than the CABG arm. This can also be seen in the NOBLE trial, for example, where at 1 year there are more deaths in the surgical arm than the percutaneous arm (17 with CABG vs nine with PCI). The longer-term results, however, show a catch-up phenomenon, with 54 deaths in the PCI group and 50 in the CABG group.

Therefore, it has been argued that long-term follow-up is essential to determine the true effects of each therapy and to better inform therapeutic decision-making. This information is now available, with longer-term results from these three large-scale randomized trials comparing outcomes with PCI and CABG in patients with left main coronary artery disease.

INDIVIDUAL CLINICAL ENDPOINTS AND THEIR IMPORTANCE TO PATIENTS

The primary outcome measures of all randomized trials comparing PCI and CABG are composite endpoints. This is necessary to reduce the required sample size and trial costs, but there are also potential issues. First, each trial does not have a uniform definition of the composite endpoint it will use as its primary outcome. Second, the individual components may also have varied definitions (with the exception of mortality endpoints). Third, each component is given equal weighting, meaning a revascularization procedure can be rated as equal to death.

EXCEL IN FOCUS

For a deeper analysis of the issues surrounding the EXCEL trial, please see our expanded News coverage on page 24.



What is the controversy regarding the EXCEL trial?

In summary, there have been accusations made about the alleged concealment of data during the conduct and publication of the EXCEL trial.

Specifically, it has been alleged that trial authors concealed the secondary endpoint of myocardial infarction (adjudicated by the so-called Universal Definition) being higher in patients treated with PCI as opposed to CABG. Furthermore, critics of the trial believe the increased rate of all-cause mortality within the PCI arm at 5 years has been underreported and warrants further scrutiny.

Ultimately, these concerns have led to the withdrawal of support by the European Association for Cardio-Thoracic Surgery for the treatment guidelines for left main coronary artery disease.

What are the key points to remember?

First and foremost, my main concern is how this well-publicized disagreement between surgical and interventional fields may affect patients who have either undergone (or are about to undergo) left main PCI. At a time when such patients are looking to their cardiologist or surgeon for impartiality and professionalism, my concern is that in the age of round-the-clock news, appropriate scientific discourse and process cannot be adequately summarized in a short news piece.

Personally, it is the totality of the evidence (SYNTAX, PRECOMBAT, and NOBLE) that reassures me of the role of PCI for left main coronary artery disease. Like the treatment guideline writers, I do not have concerns regarding the safety and efficacy of stent technologies in the left main coronary artery. Nevertheless, the controversy surrounding EXCEL has simply highlighted to me the importance of working as part of a multidisciplinary heart team and ensuring patients are actively involved in their treatment planning.

Christopher Cook, BSc, MBBS, MRCP, PhD

Imperial College London
London, United Kingdom

Individual trials will, therefore, inherently be underpowered to detect differences in individual clinical endpoints. We must either appraise each trial's primary (composite) endpoint individually, or we must turn to meta-analytical techniques to synthesise and pool results across trials for individual endpoints. Meta-analyses comparing PCI with CABG for left main disease are likely to show no differences in mortality at long-term follow-up, but their results are awaited.

RECENT CONTROVERSY REGARDING THE EXCEL TRIAL: IMPLICATIONS FOR CLINICAL GUIDELINE RECOMMENDATIONS

Recently, there has been the unprecedented step by the European Association for Cardio-Thoracic Surgery (EACTS) of withdrawing support for the 2018 joint European Society of Cardiology/EACTS guidelines on myocardial infarction due to perceived controversies and concerns regarding the EXCEL trial. One principle concern was the finding of excess mortality after PCI when compared with CABG. As previously discussed, mortality was a secondary endpoint of this trial, and the trial was not adequately powered to detect significant differences in all-cause mortality. Moreover, the difference was driven by noncardiac deaths with an unclear mechanistic explanation; there was no significant difference in cardiac deaths between the two groups. Furthermore, other trials have not demonstrated a difference in all-cause mortality between PCI and CABG at long-term follow-up. The EXCEL trial leadership officially responded to concerns raised regarding the trial with a 3,500-word statement addressing the "misleading narrative questioning the conduct of the EXCEL trial."⁸

Therefore, it would appear that the current guideline recommendations are appropriate and do not require revision or retraction.

WHAT SHOULD WE DO IN CLINICAL PRACTICE?

All trials comparing PCI and CABG in the domain of left main coronary artery disease were conducted in the context of a heart team decision that revascularization could be achieved via either modality. Therefore, collaboration between surgeons and cardiologists in the heart team should be the cornerstone of all therapeutic decision-making.

Patients should also be adequately counselled regarding all data in this field, and they should also be

reassured that there are now two safe and effective therapies for left main coronary artery disease. For those deemed at prohibitively high surgical risk, who may have previously gone untreated, PCI presents an excellent option. For patients at lower levels of surgical risk, several factors can weigh into the decision-making process. Patients with diabetes might be better served with CABG, as might those with complex multivessel disease and high SYNTAX scores. Patients should also be counselled that repeat procedures are more common after PCI than after CABG. For those who value early ambulation and discharge, with shorter recovery times, PCI might be the preferred modality, provided it is carried out by expert hands and preferably in high-volume centers with modern technology and techniques, including intracoronary imaging.

Ultimately, patients with left main coronary artery disease should be equipped with the information to choose their own treatment, with the knowledge that the totality of the randomized trial data suggest no difference in long-term survival after treatment with either PCI or CABG. ■

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;60:e44-e164.
2. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
3. EACTSJM A. EACTS responds to BBC Newsnight's investigation on the EXCEL trial. EACTS 2019. <https://www.eacts.org/eacts-responds-to-bbc-newsnight-investigation-on-the-excel-trial>. Accessed December 15, 2019.
4. Thuijs DJFM, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019;394:1325-1334.
5. Holm NR, Mäkilä T, Lindsay MM, 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.
6. Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. 2019;381:1820-1830.
7. Morice M-C, 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;129:2388-2394.
8. TCT MD. Official response from EXCEL leadership. <https://www.tctmd.com/slide/official-response-excel-leadership>. Published December 12, 2019. Accessed February 7, 2020.

Yousif Ahmad, MD

Advanced Fellow in Complex and High-Risk
Percutaneous Coronary Intervention
Columbia University Medical Center/NewYork-
Presbyterian Hospital
New York, New York
ya2431@cumc.columbia.edu
Disclosures: None.