

Why NOBLE and EXCEL Are Consistent With Each Other and With Previous Trials

The optimal management of patients with left main coronary artery disease (CAD) has been the subject of intense investigation for decades. Since the Yusuf meta-analysis of 1994 that demonstrated the survival advantage of coronary artery bypass grafting (CABG) surgery over medical management alone, clinical practice has often favored revascularization-based approaches.¹ Over the past decade, improvements in stent technology and advances in medical therapy have led to clinical trials comparing CABG, the gold standard, with percutaneous coronary interventions (PCI). At the 2016 Transcatheter Cardiovascular Therapeutics annual meeting held in Washington, DC, 2 important clinical trials comparing PCI with CABG for left main CAD were presented and simultaneously published. These studies were the NOBLE trial (Nordic-Baltic-British Left Main Revascularization),² and the EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization).³ Both trials had a noninferiority design, attempting to demonstrate that the experimental treatment, PCI, was not substantially worse than the control treatment, CABG, within a predefined acceptable extent of clinical difference based on both statistical reasoning and clinical judgment. At first glance, the apparently disparate findings of these trials may have triggered a perfect storm for guideline panelists; however, it is our opinion that the findings from these 2 trials are consistent with each other and with other modern trials that compared PCI with CABG for the treatment of advanced CAD.

The NOBLE study reported that PCI was inferior to CABG with regard to the primary end point of major adverse cardiac and cerebrovascular events, with 46% excess hazard with PCI over CABG at 5 years ($P=0.01$).² Criticisms formulated about NOBLE include the use of a biolimus-eluting biodegradable stent in the PCI group, even though recent, large trials have shown its clinical results to be comparable to those of everolimus- and zotarolimus-eluting stents. A second criticism of NOBLE was the exclusion of periprocedural myocardial infarction (MI) from the primary end point. The NOBLE investigators justified this on the basis that the Society for Cardiovascular Angiography and Interventions had not yet produced its consensus definitions between “MI of uncertain prognostic importance” and its “new definition for clinically relevant MI” at the time that the study was designed.⁴ Notably, prior trials of PCI versus CABG had not identified periprocedural MI as a driver of long-term outcome differences between these 2 modalities. Third, NOBLE was criticized for a high incidence of stroke in the PCI group; however, this phenomenon occurred beyond 1 year postrandomization, was not statistically significant, and was not responsible for the difference in primary outcome in favor of CABG.

This brings us to the larger EXCEL trial, which planned to enroll 2634 patients and closed with 1905 randomly assigned subjects after slower-than-expected recruitment.³ In comparison, NOBLE planned for and recruited 1200 patients, observed them longer (to 5 years of follow-up), and adjudicated about as many deaths, stroke, or spontaneous (ie, nonprocedural) MI events. As of this writing, NOBLE and EXCEL

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have comparable statistical power and inferential leverage.

The EXCEL study showed that the primary composite end point event of death, stroke, or MI at 3 years occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group ($P=0.02$ for noninferiority; $P=0.98$ for superiority; hazard ratio, 1.00).³ However, the noninferiority in EXCEL was driven by a lower incidence of periprocedural MI at 30 days in the PCI arm over the CABG group (3.6% versus 5.9%, respectively; $P=0.02$). In a landmark analysis, the hazard for death, stroke, or MI after 30 days was 44% higher in the PCI versus the CABG group ($P=0.02$), a figure consistent with the 46% excess hazard ($P=0.01$) observed in NOBLE.²

To our knowledge, EXCEL is the first major trial comparing PCI with CABG that used the new periprocedural MI definition for PCI outlined in the aforementioned Society for Cardiovascular Angiography and Interventions document, which shares lead authorship with EXCEL.⁴ In this regard, EXCEL used a new, higher minimum enzyme release threshold, at 10 times the upper limit of normal, to independently adjudicate the occurrence of a periprocedural MI around PCI. If the resultant relative excess in periprocedural MIs in the CABG group of EXCEL had important clinical significance (eg, indicating incomplete revascularization, a blocked graft, resultant scar, or left ventricular dysfunction), one would have anticipated observing higher rates of subsequent death or MI in this group. Rather, the opposite result, with higher event rates in the PCI group, was seen during follow-up (Figure).³

It is also important to distinguish between isolated left main coronary artery stenosis and left main disease accompanied by more extensive and multivessel involvement. In this regard, the key question that comes to mind is not only how to optimally manage the left main lesion, but also how management should vary with the presence of additional, multivessel CAD. Both NOBLE and EXCEL are underpowered in their assessment of these important subpopulations, and trends will need to be examined in well-conducted meta-analyses of all key trials comparing PCI and CABG.

Recently, 1 meta-analysis examined the results of PCI versus CABG for unprotected left main coronary artery stenosis.⁵ The pooled data were numerically leveraged by EXCEL and varied in their definition of periprocedural MI. The authors presented a neutral result for the primary end point of all-cause death, MI, or stroke (odds ratio, 0.97; 95% confidence interval, 0.79–1.17; $P=0.73$). Despite incorporating a similar periprocedural MI definition as was used in EXCEL, a trend toward more MIs with PCI than with CABG was observed (odds ratio, 1.46; 95% confidence interval, 0.88–2.45; $P=0.08$), and PCI was inferior for the primary end point in patients with a SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score ≥ 22 (odds ratio, 1.64; 95% confidence interval, 1.22–2.20; $P=0.006$).

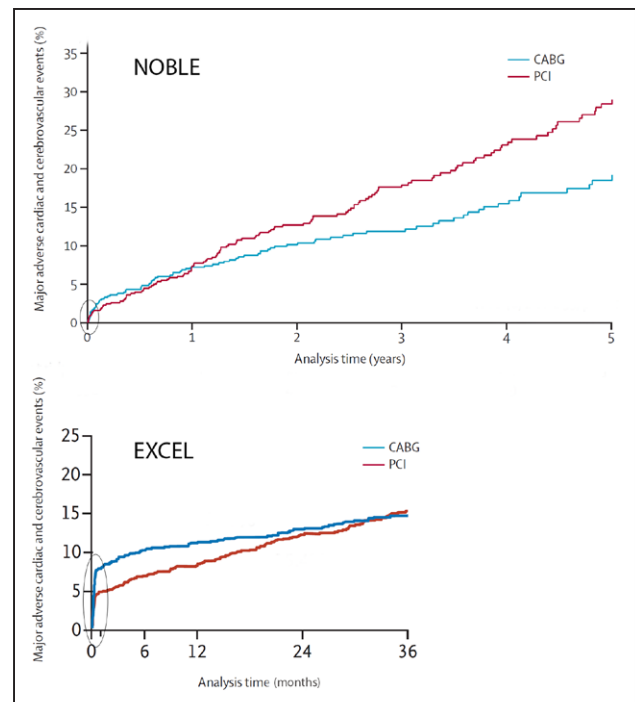


Figure. Rates of the primary end point event of death, myocardial infarction, or stroke, in the Nordic-Baltic-British Left Main Revascularization (NOBLE) trial² and in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial,³ at 5 and 3 years of follow-up, respectively.

A new periprocedural MI definition was used in EXCEL, and the 2 studies differed in their inclusion of periprocedural MI in the composite primary end point, resulting in early outcome differences (circles) in EXCEL but not in NOBLE. Outside the periprocedural period, the event rate slopes of the respective PCI and CABG groups across both studies are remarkably similar. NOBLE reported that PCI was inferior to CABG at 5 years, whereas EXCEL indicated that PCI was noninferior to CABG at 3 years. CABG indicates coronary artery bypass grafting; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Overall, we believe that the results of EXCEL to date are consistent with those of NOBLE, and with previous data from the SYNTAX trial and FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), where trends in favor of CABG have taken between 2 and 3 years to emerge. As depicted in the Figure, in EXCEL, a new, higher threshold to adjudicate a periprocedural MI in the PCI group resulted in a sizable difference at the beginning of the event rate slopes. However, during follow-up, the slopes of the primary end point rates (death, MI, or stroke) for each treatment arm in EXCEL are remarkably consistent with those observed in NOBLE.

In conclusion, EXCEL does not refute the conclusions of other recent trials on the treatment of left main coro-

nary artery stenosis (NOBLE, SYNTAX), or trials of more advanced multivessel CAD (FREEDOM, BEST [Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease]). Taken together, EXCEL and NOBLE again confirm that CABG is the most robust and durable therapy for coronary revascularization in the presence of advanced CAD. The next big question in coronary revascularization should not focus on PCI versus CABG, but rather on ways to improve outcomes for PCI and CABG patients alike by optimizing background medical therapy and by individualizing their care.

DISCLOSURES

None.

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FOOTNOTES

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