The controversy on the treatment of left main coronary artery disease

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The last few years have witnessed a heated debate within the cardiovascular community on the most appropriate treatment for left main coronary artery disease (LMCAD), mainly due to apparently contradictory results and interpretations of the 2 largest randomized clinical trials. In this review, we summarize the controversy and critically evaluate the available evidence.

IS LMCAD A SEPARATE ENTITY?

A key first step to address the conundrum would be to understand whether the available data support the concept that LMCAD is a separate entity within the broader spectrum of coronary artery disease (CAD). In the largest individual patient data meta-analysis of randomized clinical trials comparing coronary bypass surgery (CABG) with percutaneous coronary interventions (PCIs) in patients with multivessel coronary disease (MVD) or LMCAD, 5-year all-cause mortality was significantly increased in patients who received PCI (11.2% vs 9.2% after CABG; hazard ratio [HR], 1.20; 95% confidence interval [95% CI], 1.06-1.37; $P = .003$).¹ LMCAD was not a significant treatment effect modifier, implying that the main result of the analysis (CABG associated with lower mortality) remains valid even in patients with LMCAD.¹

Anatomically, isolated LMCAD has historically represented a small subset of CAD. In the Coronary Artery Surgery Study registry, isolated LMCAD was found in 1477 of 20,137 patients (7.3%).² LMCAD is mainly a manifestation of MVD, as shown by its frequent association with MVD and the need for revascularization of the other coronary beds in approximately 50% of cases.^{3,4}

Therefore, the concept that LMCAD is as a separate entity that requires specific recommendations seems poorly supported by the available data, and instead an approach to LMCAD that is consistent with the evidence acquired in the treatment of MVD seem more appropriate.

A BRIEF HISTORY OF THE TREATMENT OF LMCAD

CABG was initially considered the standard of care for CAD, including LMCAD, based on the positive results of trials that compared surgery with medical therapy in the

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CENTRAL MESSAGE

Left main coronary artery disease is not a separate entity and should be treated preferentially with surgery based on the totality of the cumulated evidence.

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1970s and 1980s.⁵ An 2009 publication of individual patient data from 10 randomized trials comparing CABG with PCI, using angioplasty alone (6 trials) or bare metal stents (4 trials) in MVD, showed a statistically nonsignificant 1% decrease in mortality at 5 years' follow-up with CABG.⁶ These results are now of primarily historical interest, as they do not reflect current surgical and interventional cardiology standards nor currently treated populations and therefore are of limited contemporary value.

The Synergy between percutaneous coronary intervention with Taxus and Cardiac Surgery (SYNTAX) trial was the first adequately powered trial to compare the 2 treatments in the modern era and set the foundation for the design of future trials in this field.⁷ This trial randomly assigned 1800 patients with 3-vessel or LMCAD in whom equivalent anatomical revascularization could be achieved to undergo CABG or PCI. The primary end point was a composite of death from any cause, stroke, myocardial infarction (MI), or repeat revascularization (RR) at 12 months' follow-up. There were significantly more composite end points in the PCI group (17.8%, vs 12.4% for CABG; $P = .002$) and therefore noninferiority was not established. The SYNTAX protocol included a prespecified secondary analysis of LMCAD that was powered to 80%. However, as the primary hypothesis of noninferiority was not established, secondary outcomes for each subgroup

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are properly considered only as hypothesis-generating. Nevertheless, the secondary end point of LMCAD outcomes at 5 years again favored CABG in absolute term, although the difference did not reach statistical significance (36.9% in patients who underwent PCI and 31.0% in patients who underwent CABG: HR, 1.23; 95% CI, 0.95-1.59; $P = .12$). The benefit of surgery was compelling for patients with anatomical high complexity CAD, with 1-year primary event rates of 23.4% in the PCI group versus 10.9% in the surgical, such that future LMCAD hypothesis testing trials have been limited to cases with low and medium coronary disease complexity.

The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRE-COMBAT)⁸ trial was a small (300 patients) trial that used a wide noninferiority margin (absolute risk reduction of 7% at 1 year in the composite of death from any cause, MI, stroke, or ischemia-driven target-vessel revascularization) and, as acknowledged by the authors, was too limited in sample size to be considered clinically relevant.

THE EXCEL VERSUS NOBLE CONTROVERSY

Two large trials were next designed to specifically evaluate the choice of revascularization technique in LMCAD with low and medium coronary disease complexity: the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and the Nordic-Baltic-British left main revascularisation (NOBLE).^{3,4} Although both used a noninferiority approach with similar boundaries (4.0% in NOBLE and 4.2% in EXCEL), the 2 trials made different choices regarding their primary composite outcome measures. NOBLE used as the primary end point a composite of death from any cause, nonprocedural MI, RR, and stroke, whereas EXCEL included periprocedural MI but excluded RR from the primary composite outcome.

The choice not to include RR was justified by the EXCEL investigators due to a potential ascertainment bias and their opinion regarding the uncertain clinical significance of a repeat revascularization.⁹ However, RR is significantly associated with clinical events in modern CABG versus PCI trials¹⁰ (including EXCEL)¹¹ and is certainly associated with an impact on overall quality of life, so its exclusion from the primary composite outcome may be debated. EXCEL also used a new definition of periprocedural MI that allows a purely enzymatic diagnosis of MI and inherently disadvantages CABG due to the postoperative enzymatic increase related to the surgical manipulation of the heart.¹² In fact, the rate of perioperative MI reported in the surgical arm in EXCEL was double than in other CABG versus PCI trials,⁷ including the SYNTAX trial, which included many of the same centers. The absence of MI data based on the Universal Definition (a prespecified secondary end point) in the original

3- and 5-year EXCEL publications has been problematic in comparing results across different trials.

The lead EXCEL authors in a paper on the methodology of revascularization trials had previously discouraged the use of enzymatic outcomes.¹³ Moreover, the long-term prognosis of periprocedural MIs seems more benign than later nonprocedural MIs, supporting the NOBLE decision to exclude these early periprocedural events.^{14,15} One could argue that the choices of the EXCEL investigators with regard to the components of their primary outcome seem contradictory: on one end, they exclude RR because they do not consider revascularization an hard clinical end point, but on the other end they adopt a purely enzymatic definition of MI rather than the Universal Definition (that is based on the clinically meaningful demonstration of ischemia).

From the aforementioned, one can appreciate the difficulties in defining a primary composite end point and how these differences in design can contribute to differences in the results between trials, a consideration that is particularly important when trials are sponsored or designed by industry.^{16,17} Reasonable arguments can be made to support each of these different choices, underscoring the importance of systematically collecting and making fully available the totality of the evidence.

At 5-year follow-up, NOBLE reported CABG superiority for their primary composite outcome (HR, 1.58; 95% CI, 1.24-2.01) and for MI (HR, 2.99; 95% CI, 1.66-5.39) and RR (HR, 1.73; 95% CI, 1.25-2.40, respectively).³ In contrast, EXCEL reported no difference between the 2 arms for the primary composite outcome (22% vs 19.2%, difference, 2.8 percentage points; 95% CI, -0.9 to 6.5; $P = .13$), but a significant difference in favor of surgery for their secondary outcomes of mortality (13.0% vs 9.9%; difference, 3.1 percentage points; 95% CI, 0.2-6.1) and RR (16.9% vs 10.0%; difference, 6.9 percentage points; 95% CI, 3.7-10.0).⁴ The 2 MI outcomes in EXCEL (periprocedural and spontaneous) moved in opposite directions, suggesting that they are looking at different biological phenomena and rendering their combined interpretation problematic (Figure 1). Periprocedural MI was the only outcome more frequent in the CABG arm, being largely responsible for the reported null result of the EXCEL primary composite outcome. The EXCEL authors published the Universal Definition MI data in a post-publication letter to the editor.¹⁸ Importantly, the overall MI rates using the Universal Definition were 9.6% with PCI and 4.7% with CABG (difference, 4.9 percentage points; 95% CI, 2.6-7.2). If the EXCEL primary composite outcome is recalculated using the Universal Definition MI data, it is significantly in favor of surgery (Figure 1). Also, when the Universal Definition is used, the difference in perioperative MI is in favor of CABG, not PCI (3.3% vs 1.4%, difference, 1.9 percentage points; 95% CI, 0.5-3.3, Figure 1).

FIGURE 1. ORs for the major primary and secondary outcomes in EXCEL at 5 years. All the cardiac outcomes, with the only exception of perioperative myocardial infarction based on the EXCEL definition, favor surgery. The OR for the primary outcome using the UD data are calculated based on the number of events provided in the EXCEL manuscript and correspondence. We acknowledge that our approach has limitations due to counting of multiple events from the same patients. However, (1) there is no biologic reason why this should affect one group more than the other and (2) when using the same methodology to recalculate the odds ratio (OR) for the composite of death, stroke or myocardial infarction, our estimate (1.24 [0.99-1.53]) is very close to that obtained using the time-to-first-event analysis in EXCEL. Data not presented in the original EXCEL manuscript are in red. PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; CI, confidence interval; UD, universal definition.

The EXCEL mortality difference (13.0% PCI vs 9.9% CABG) was concerning, as not only was the result both of a clinical and statistical meaningful magnitude but also the survival curves appeared to be continuing to diverge in favor of CABG at 5 years. As the mortality difference was reported to be largely secondary to an excess in noncardiac events, the EXCEL investigators attributed this as likely a chance occurrence. However, the problems with adjudication of the cause of death in clinical trials is well known¹⁹ and this significant difference in mortality raises major concerns.

Finally, while EXCEL was originally designed and analyzed at 3 years as a noninferiority study, the EXCEL investigators reported their 5-year results in a superiority rather than a noninferiority context. If the 5-year data are analyzed using the original EXCEL noninferiority margin of 4.2%, the null hypothesis of PCI being inferior to CABG would not have been rejected, and the overall conclusions of NOBLE and EXCEL at 5 years would have been seen as concordant.

THE ROLE OF STANDARD FREQUENTIST META-ANALYSIS TO UNDERSTANDING THE CONTROVERSY

Not surprisingly, several aggregate trial level meta-analyses pooling different combination of the recent LMCAD trials have been published.²⁰ The results have generally shown a long-term benefit for CABG at the price of a greater periprocedural risk, although final interpretations have varied according to different authors. The results

of meta-analyses are highly dependent on inclusion criteria and outcomes definitions and, unfortunately, cherry picking of both and reporting bias (“spin”) have been well described, in particular for research questions with important financial consequences for industry.^{17,21,22}

For example, a recent meta-analysis concluded “The totality of randomized clinical trial evidence demonstrated similar long-term mortality after PCI with DES compared with CABG in patients with LMCAD. Nor were there significant differences in cardiac death, stroke, or MI between PCI and CABG.”²³ Of note, all the authors of this positive view of PCI for LMCAD were interventional cardiologists, and the presentation of the results may be seen as slightly disingenuous, as none of these trials were powered for these individual end points. Consider the outcome of MI where the PCI results were RR, 1.22; 95% CI, 0.96-1.56; $P = .11$. Now a simplistic conclusion is that no difference exists between the 2 techniques, but this is only correct if one is willing to accept that a potential 56% increase in the risk of MI with PCI is clinically inconsequential. Otherwise, the pithy epithet “absence of evidence is not evidence of absence” would appear applicable. The fact that this manuscript timeline from submission to revisions to acceptance was only 11 days (even more remarkable as it happened in the middle of the coronavirus disease 2019 crisis) also suggests the possibility of confirmation or group think bias.

It has been proposed that an individual patient level meta-analysis should be the final arbitrator to the LMCAD conundrum. We agree that the principles of data sharing

underlining individual patient level meta-analyses are scientifically desirable, but study-specific caveats apply before such analyses can be sensibly interpreted. Specifically, for the LMCAD controversy, data sharing should be entirely open to the whole scientific community and not restricted only to highly selected and opinionated subgroups of researchers. Second, this design demands an interdisciplinary approach with diversified content experts and methodologic experts, as data harmonization is essential and may pose significant hurdles.²⁴ For example, the heterogeneity in the definitions of MI, discussed previously, is potentially very problematic. Other issues with individual patient level, as well as aggregate meta-analyses, involve data (trial) selection that can lead to both clinical bias, as the old trials are not reflective of the current practice, and methodologic bias, as the early exploratory trials typically overestimate the treatment effect.²⁵ Finally, individual patient level meta-analyses can still be subject to various interpretative biases. For example, an individual patient level meta-analysis concluded “CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease.”¹ This interpretation may be questioned, as the interaction test was not significant and the analysis did not allow individual covariates to vary randomly across clusters and employed null hypothesis significance testing which views results in a restrictive dichotomized manner.²⁶ A Bayesian approach may address the latter concerns as well as allowing the inclusion of case specific prior information in an open, transparent and probabilistically coherent manner.

IS A BAYESIAN REANALYSIS THE BEST APPROACH?

The individual data from the current trials have not been made available for open analyses and therefore a Bayesian meta-analysis is limited to the aggregate approach. A Bayesian analysis has several advantages over the standard null hypothesis statistical testing (NHST). Mechanistically this involves updating our previous beliefs about a parameter estimate, for example, the difference in outcomes between the CABG and PCI, with new data to provide a final (posterior) probability distribution. Bayesian analyses acknowledge the uncertainty around any parameter estimate and permit the formation of direct probability statements that follow incontrovertibly the laws of probability. Such an approach also avoids the NHST cognitive pitfalls of dichotomania and nullism²⁷ and instead, by providing probabilities of clinically desirable parameters, may lead to additional insights.

A Bayesian analysis uses the previous CABG/PCI trial results, including NOBLE, as informative previous evidence, and update this with the EXCEL results to produce a posterior probability distribution of the comparative

benefits that accounts for the totality of the evidence and its associated uncertainty. While the most recent frequentist meta-analysis succinctly, and simplistically, concluded that no mortality difference existed between PCI and CABG, the Bayesian analysis has suggested that the probability of increased mortality with PCI for LMCAD was 85%, with a 47% probability that this increase was greater than 1 extra life lost per 100 treated.²⁸ The most likely estimate was 9 lives lost per 1000 with PCI and 95% credible intervals from 8 lives saved and 27 lives lost per 1000. It is arguable that an accompanying graphic presentation of this mortality data (Figure 2) is more informative than the standard frequentist view, as it permits easy recognition of the cumulative nature of knowledge and easy calculations of the posterior probability that differences exceed varying thresholds.

Consider the following simple analogy to underscore the relative merits and “actionable” outcomes following a Bayesian analysis. The null hypothesis is “it will not rain today.” The standard NHST approach analyses the available data and concludes that the null hypothesis can’t be rejected. What is the “actionable” outcome from this analysis? Most would concur it would be to not take an umbrella. The Bayesian examines the same data and concludes there is an 85% (updated probability) of rain today and a 47% that it will be a deluge. What is now the “actionable” outcome? For many people, it would be to take an umbrella. In our opinion, the transparency of the Bayesian approach provides sharp contrasts with the frequentist approach and is more informative for physicians and, most importantly, for patients. The Bayesian approach may, depending on personal values and risk assessment, indeed lead to different shared “actionable” decision-making by patients and their physicians.

As a further demonstration of the Bayesian ability to quantify parameter estimations and their uncertainty and improve data understanding, consider the composite primary outcome of most LMCAD revascularization trials, all-cause mortality, non-fatal MI, and stroke. The Bayesian approach reveals a 96% probability that this outcome is decreased with CABG with a most likely estimate of avoiding 2.6 events/100 treated (95% credible interval, -0.33% to 5.6%) compared with PCI (Figure 2, B). An analysis that included repeat revascularizations in the composite endpoint estimates a 98% probability of at least 4 fewer events per 100 treated with CABG.²⁸

CONCLUSIONS

In conclusion, convincing evidence from multiple randomized trials suggests that LMCAD is not a separate entity within the spectrum of MVD and consequently should be treated based on the totality of the cumulated evidence. This evidence concordantly shows that CABG is associated with improved patients’ outcomes, including a reasonably

FIGURE 2. Bayesian triplots. Probability density plots of prior beliefs, current data (likelihood), and the posterior beliefs, including EXCEL, NOBLE, and PRECOMBAT. The posterior distributions are represented by a weighted average of the prior and likelihood distributions. Our increasing knowledge is reflected by a narrowing of the posterior distribution. The flexibility of Bayesian analyses permits a straightforward calculation of the posterior probability exceeding any given threshold by a simple calculation of the AUC to the right of the selected threshold. A, Probability density functions for the prior evidence, the current data (likelihood), and the combined (posterior) distributions for the outcome of total mortality. The posterior probability of increased mortality with PCI is therefore 85%. B, Probability density functions for the previous evidence, the current data (likelihood) and the combined (posterior) distributions for the primary composite outcome. The posterior probability of an increased primary composite outcome with PCI is therefore 96%. *AUC*, Area under the curve; *SYNTAX*, synergy between percutaneous coronary intervention with taxus and cardiac surgery; *NOBLE*, Nordic-Baltic-British left main revascularisation; *PRECOMBAT*, premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease; *EXCEL*, evaluation of XIENCE versus coronary artery bypass surgery for effectiveness of left main revascularization; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

high probability of decreased mortality, and should therefore be the standard of care in patients who are at acceptable surgical risk and who have a reasonable life expectancy. Current Guidelines that do not represent this contemporary state of our knowledge need to be urgently addressed.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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