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EDITORIAL

Ten-Year Follow-Up of Left Main Coronary Artery Revascularization

Still Equipoise Between Percutaneous Interventions and Surgery?

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Fernando Alfonso, MD, PhD
Adnan Kastrati, MD, PhD

Left main coronary artery disease (LMCAD) remains a therapeutic challenge with important prognostic implications attributable to the large amount of subtended myocardium.[1,2] The current European clinical practice guidelines on coronary revascularization provide the same level of recommendation (class IA) for percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for patients with LMCAD with low anatomic complexity (SYNTAX [Synergy between PCI with Taxus and Cardiac Surgery] score ≤22).[2] However, CABG is considered superior to PCI (class IA versus IIIB) for patients with LMCAD and severe complexity.[2] This represents a paradigm shift considering that only a decade ago elective PCI was contraindicated (class III) for any patient with LMCAD eligible for CABG.[1] Two recent randomized clinical trials (RCTs) using contemporary techniques in patients with LMCAD provided new but conflicting data.[3,4] Both studies used new-generation drug-eluting stents (DES) in the PCI arm. The NOBLE trial (Nordic–Baltic–British Left Main Revascularisation Study) (primary end point: composite of death, nonprocedural myocardial infarction [MI], repeat revascularization, and stroke at 3.1 years) suggested that CABG should remain the therapy of choice in this setting.[3] However, the larger EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (primary end point: composite of death, MI, and stroke at 3 years) suggested that, in patients with LMCAD and low-to-moderate anatomic complexity (SYNTAX score ≤32), PCI with everolimus-DES was noninferior to CABG.[4] Of note, in EXCEL PCI was also noninferior to CABG when ischemia-driven target-vessel revascularization (TVR) was included in the combined end point.[4] The controversy was recently refueled by the publication of the 5-year results of these trials that basically confirmed their initial results but showed additional discordant data, including all-cause mortality (higher with PCI in EXCEL, but similar in NOBLE) with a similar cardiac mortality with both strategies in both studies.[5,6] The differences in MI rates also generated methodological concerns (periprocedural MI not assessed in NOBLE, MI definition questioned in EXCEL).[5,6] For the first time ever, disagreements between the scientific societies of cardiac surgeons and cardiologists reached the lay press, generating confusion and some alarm in related stakeholders and, importantly, in patients.

Accordingly, additional information on the very long-term results of these revascularization strategies, in particular, if coming from rigorous well-designed RCTs, is welcome to inform the clinical decision-making process in patients with LMCAD.

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

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THE CURRENT STUDY

In this issue of *Circulation*, Park et al[7] present the extended (>10 years) clinical follow-up (median, 11.3 years) of the PRECOMBAT RCT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) that compared clinical outcomes after revascularization (sirolimus-DES n=300 versus CABG n=300) in patients with unprotected LMCAD treated in 13 Korean sites from 2004 to 2009. One-third of patients had diabetes mellitus and two-thirds had distal bifurcation LMCAD and multivessel disease (mean SYNTAX score, 24.8). Patients were considered equally suitable for both strategies, and the rate of complete revascularization was actually similar in both arms. At 1 year, PCI was noninferior to CABG.[8,9] At 10 years, the primary outcome measure (a composite of death, MI, stroke, or ischemia-driven TVR) occurred in 29.8% in the PCI group and 24.7% in the CABG group (hazard ratio, 1.25 [95% CI, 0.93–1.69]). Likewise, the 10-year incidence of a composite of death, MI, or stroke (18.2% versus 17.5%) and all-cause mortality were not significantly different between the groups. However, ischemia-driven TVR was 2-fold higher after PCI (16.1% versus 8.0%).[7]

The extended clinical follow-up (96% patients with a follow-up >10 years) of this pivotal trial strongly suggests that revascularization with PCI or CABG provides similar long-term clinical outcomes in these patients. The study by Park et al represents the longest follow-up ever reported in a large RCT specifically designed to compare revascularization modalities in patients with LMCAD. Considering the potential clinical implications of these important findings, addressing some methodological issues would be of interest.

First, despite the meritorious extended clinical follow-up, the study remains largely underpowered for its primary end point. This is nicely acknowledged by the investigators, suggesting that results should not be considered definitive but rather hypothesis generating. Nevertheless, the lack of differences in the primary outcome (that included TVR) in the intention-to-treat analysis is highly reassuring. However, further studies with very long-term follow-up are still required to confirm the clinical equipoise between these revascularization strategies.

Second, CABG was superior to PCI for the primary end point in both as-treated and per-protocol analyses. These sensitivity analyses are important in studies with a noninferiority design, consider crossovers, and may better reflect everyday clinical practice. It is reassuring that the combined outcome of death, MI, or stroke remained similar with both strategies in these analyses, because the difference was driven by the TVR rate. However, further insights on the potential clinical implications of these divergent findings should be provided to dissipate potential doubts on the equivalences of these competing strategies in routine clinical practice.

Third, the predefined subgroup analysis was consistent with the main results, with the exception of the subset of patients with associated 3-vessel disease (41% in both arms) where CABG was superior. These findings confirm previous evidence supporting the superiority of CABG over PCI in patients with LMCAD and concomitant severe coronary artery disease.[1,2] However, a treatment interaction with the SYNTAX score was not found for the primary end point, although the rate of TVR was higher with PCI in patients in the high SYNTAX tertile. In this study, the SYNTAX score was obtained post hoc in a centralized core laboratory. Likewise, diabetes mellitus status had no interaction with the treatment effect. This appears difficult to reconcile with the large body of evidence supporting the superiority of CABG over PCI for diabetic patients with advanced coronary artery disease. Additional granularity on the influence of diabetes mellitus on the individual components of the primary end point would have been of value. Although previous studies demonstrated that diabetes mellitus status and SYNTAX score are major treatment effect modifiers in patients with multivessel disease, their influence in patients LMCAD remains controversial.[10]

Fourth, by study design, late angiographic surveillance (8–10 months) was systematically scheduled only in the PCI arm. This is no longer recommended[2] and is potentially relevant, because TVR (the main difference between the 2 strategies) is significantly affected by this practice. A close look to the TVR actuarial survival curves reveals that they start to diverge precisely at this time. Moreover, ischemia-driven TVR included procedures performed in asymptomatic patients with angiographically severe (>70% diameter stenosis) lesions. Therefore, the potential role of the oculostenotic reflex penalizing the PCI arm remains difficult to ascertain.

Fifth, procedural-related issues are of paramount importance. In the CABG group, the internal thoracic artery was used for the left anterior descending coronary artery in 94% of patients, whereas 64% underwent off-pump surgery. Conversely, only first-generation DES were used in the PCI arm. There is a large body of evidence suggesting that new-generation DES are not only safer (risk of thrombosis), but also more effective (risk of restenosis) than first-generation DES.[11] Whether a more favorable clinical outcome would have been found in the PCI arm with the use of new-generation DES remains speculative. However, the favorable results found in EXCEL (where only a best-in-class new-generation everolimus-DES was used) support this possibility.[4,6]

Conversely, intravascular ultrasound was used in 91% of patients in the PCI group. This is much higher than that seen in everyday clinical practice, despite current guideline recommendations (class IIaB),[2] and could explain the excellent results obtained with first-generation DES in this study. However, the external validity of these findings remains unclear. Recent studies confirm the value of intravascular ultrasound guidance in patients with LMCAD, in particular, when well-defined prespecified optimization criteria are used.[12]

Sixth, clinical follow-up was not obtained yearly from 5 to 10 years but only at 10 years. Events were centrally adjudicated by a blinded clinical events committee and eventually, thanks to the Korean universal health coverage system, 10-year vital status could be verified in 100% of participants. However, the lack of systematic clinical follow-up between 5 and 10 years may have increased the risk of event underreporting. It remains unclear whether the relatively low event rate found in this study, in comparison with other RCTs on LMCAD, reflects a more favorable baseline clinical and angiographic (including the SYNTAX score) profile.[3,4,13]

Last but not least, a detailed analysis of long-term medication use was not provided. This should be considered when interpreting the results, because previous studies suggested that better adherence to guideline-recommended strategies tends to occur after PCI in comparison with CABG.

PREVIOUS STUDIES WITH 10-YEAR CLINICAL FOLLOW-UP

The LE MANS RCT (Left Main Stenting in Comparison with Surgical Revascularization) reported no differences in survival or events at 10 years in patients with LMCAD treated with CABG or PCI with bare-metal or first-generation DES. However, the power of this study was extremely limited, because only 105 patients were enrolled.[14] In the extended 10-year clinical follow-up of the MAIN-COMPARE observational registry (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) (including 2240 real-world patients), the composite of death, MI, or stroke was similar for PCI and surgery after adjusting for baseline characteristics.[15] However, the need for repeat TVR was higher after PCI. In this study, the SYNTAX score discriminated long-term outcomes favoring surgery in patients with complex anatomy, mainly because of its prognostic influence on the PCI group.

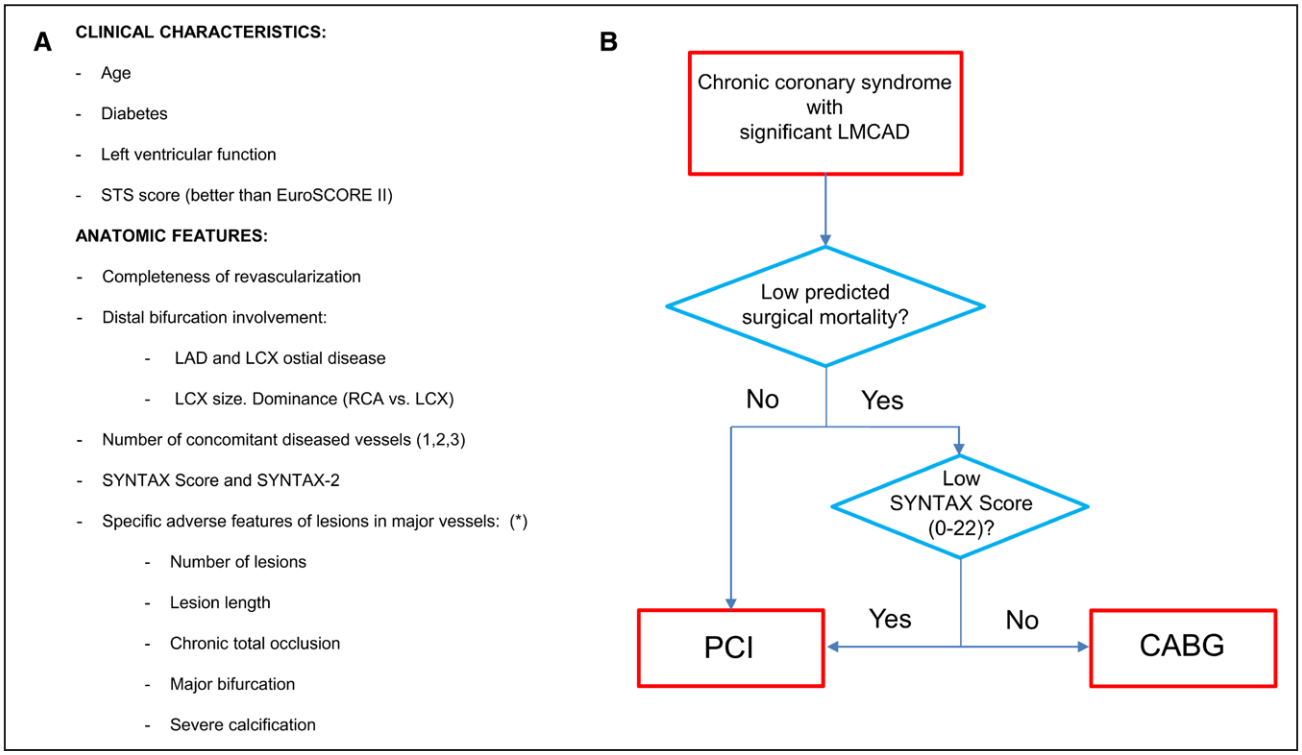

Figure. Left main coronary artery disease (LMCAD) revascularization.
A, Relevant variables to be considered in the clinical decision-making process of elective treatment of patients with unprotected LMCAD eligible for coronary artery bypass grafting (CABG). *Specific assessment of relevant individual lesion characteristics in addition to the SYNTAX score. **B**, Simplified management algorithm for patients with chronic coronary syndrome and LMCAD. This is proposed despite the controversy regarding the differential prognostic value of the SYNTAX score in patients with LMCAD (see text). In patients with a low Syntax score (equipoise), PCI (less invasive) is preferred. EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; STS, Society of Thoracic Surgeons; and SYNTAX, Synergy between PCI With Taxus and Cardiac Surgery. (Updated from Alfonso.[1])

However, selection bias and residual confounders could not be completely ruled out. In addition, bare-metal stents and first-generation DES were used. Finally, the SYNTAX extended survival study provided 10-year vital status information of patients with 3-vessel disease or LMCAD included in the SYNTAX noninferiority RCT where patients were treated with first-generation paclitaxel-DES or CABG.[13] Vital status at 10 years was obtained in 84% of the 1800 patients randomly assigned. Among the 705 patients followed in the prespecified LMCAD subgroup, 10-year mortality was similar with both revascularization techniques (26% after PCI and 28% after CABG). No interaction was found between the SYNTAX score or diabetes mellitus status and the relative treatment effect. In all these studies, only first-generation DES were used. A very recent meta-analysis of the 5 RCTs available on LMCAD (4612 patients; mean follow-up, 5.6 years) showed similar all-cause and cardiac mortality with the 2 revascularization strategies.[16] The extended follow-up of EXCEL and NOBLE, where new-generation DES were used, are eagerly expected to keep shaping this dynamic field.

FINAL REMARKS

A decade ago, we suggested that PCI had crossed the Rubicon and could be considered as the strategy of choice for elective revascularization of selected patients with LMCAD and asked for an update in the existing guidelines.[1] Since then, the accumulating body of evidence demonstrating the safety and effectiveness of PCI in patients with LMCAD has been impressive. The 10-year results of PRECOMBAT further expand our knowledge, providing compelling evidence that clinical equipoise, defined as uncertainty regarding the relative benefits of competing revascularization modalities, persists for patients with LMCAD and low-to-intermediate anatomic complexity. However, the occurrence of revascularization failure at this critical site remains of concern considering its prognostic implications. The higher need for TVR in the PCI arm, consistently seen in all LMCAD studies, overshadows the long-term results of this strategy. The current study also provides useful insights to better inform the clinical decision-making process to select the optimal revascularization modality for these patients. In every day clinical practice, the main challenge for the Heart Team remains to select the best revascularization strategy for each patient, according to individual baseline clinical and anatomic characteristics, revascularization completeness, and patient preferences (Figure).

ARTICLE INFORMATION

Correspondence

Fernando Alfonso, MD, Department of Cardiology. Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria Princesa, IIS-IP, CIBER-CV, Diego de León 62, Madrid 28006, Spain. Email falf@hotmail.com

Affiliations

Department of Cardiology, Hospital Universitario de La Princesa, Madrid, Spain (F.A.). Deutsches Herzzentrum München, Technische Universität, and the German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Germany (A.K.).

Disclosures

None.

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