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Editorial / *Editöryal Yorum*

Left main coronary disease percutaneous coronary intervention: The quest to reconcile the inconsistencies

Sol ana koroner hastalığında perkütan koroner girişim: Tutarsızlıkları uzlaştırma arayışı

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The optimal revascularization strategy for patients with left main (LM) coronary disease remains a matter of intense controversy in the cardiovascular community. Coronary artery bypass graft (CABG) surgery has traditionally been considered the gold standard revascularization modality for patients with obstructive LM disease (historically defined as a diameter stenosis of >50%) due to its established mortality benefit over medical therapy.[1] Due to significant advances in procedural techniques, iterative developments in drug-eluting stent (DES) technology, increased operator expertise, and the introduction of potent antithrombotic therapies, percutaneous coronary intervention (PCI) with newer-generation DESs has emerged as a valid alternative revascularization strategy for higher-risk patients with complex coronary artery disease (CAD), such as those with unprotected LM disease.

The available evidence from randomized clinical trials (RCTs)[2–5] and subsequent meta-analyses[6,7] that compared CABG with PCI using DES demonstrates comparable results with regards to the composite endpoint of all-cause death, myocardial infarction (MI), and stroke in up to 5 years of follow-up. These trials have, however, revealed a significant time-dependent treatment interaction, as the early benefit from PCI with respect to peri-procedural MI and stroke is subsequently offset by a higher risk of spontaneous MI compared with CABG during long-term follow-up. Two, small, randomized studies have compared CABG with PCI using first-generation DES for LM revascularization. In the LM subgroup analysis of the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) study[2] and in the Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) trial,[3] the occurrence of the primary composite endpoint of all-cause death, MI, stroke, or repeat revascularization at 5 years did not differ between patients with LM disease treated with CABG or PCI using early-generation, thick-strut, paclitaxel- or sirolimus-eluting stents, respectively, but event rates were significantly higher among PCI patients with high SYNTAX scores (≥33) compared with CABG.[2] The recent 5-year outcome results of 2 larger-scale, randomized clinical trials comparing PCI using newer-generation DES with CABG using contemporary surgical techniques for LM disease have yielded in-

Abbreviation:

CABG	*Coronary artery bypass graft*
CAD	*Coronary artery disease*
DES	*Drug-eluting stent*
IVUS	*Intravascular ultrasound*
LM	*Left main*
MACCE	*Major adverse cardiac and cerebrovascular event*
MI	*Myocardial infarction*
PCI	*Percutaneous coronary intervention*
RCT	*Randomized clinical trial*

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consistent results. The Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial randomly assigned 1905 patients with LM disease and low-to-intermediate anatomical complexity to PCI with thin-strut, durable polymer, everolimus-eluting stents or CABG.[4] At 5 years, there was no significant difference between PCI and CABG with respect to the primary composite outcome of death, MI, or stroke.[4] The findings suggesting an increased long-term risk of all-cause mortality among patients treated with PCI as compared with CABG have raised serious concerns about the safety of PCI for LM revascularization. The Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial randomized 1201 patients with LM disease to PCI with thick-strut, biodegradable polymer, biolimus-eluting stents or CABG.[5] Unlike EXCEL, NOBLE found that CABG was superior to PCI in the primary composite endpoint of all-cause death, non-procedural MI, stroke, or repeat revascularization at 5 years, but did not demonstrate significant differences in terms of mortality between CABG and PCI.[5] RCTs using primary composite endpoints are per se largely underpowered to detect differences in low-frequency individual endpoints, such as death, or MI, and these conflicting findings should therefore be interpreted with caution. Until further definite randomized evidence becomes available, these inconsistencies need to be reconciled to emphasize the importance of heart team consideration of a tailored revascularization approach for patients with LM disease. A recently updated study-level meta-analysis that included 4612 patients from 5 RCTs found no significant differences in all-cause mortality, cardiac death, MI, or stroke at a mean follow-up time of 5.6 years between patients with LM disease treated with CABG or PCI. While PCI was associated with a significantly increased risk of spontaneous MI and unplanned revascularization compared with CABG, the risk of procedural MI was higher with CABG than with PCI.[6] The current European guidelines on myocardial revascularization recommend PCI as an appropriate alternative to CABG in patients with LM disease and low (SYNTAX score 0–22) or intermediate (SYNTAX score 23–32) anatomical complexity, whereas CABG is still considered superior to PCI among patients with LM disease and high anatomical complexity (SYNTAX score ≥33).[7] The impact of coronary lesion complexity as a treatment modifier in patients undergoing LM revascularization has recently been challenged by an individual data pooled analysis including 4478 patients with LM stenosis from 4 randomized trials.[8] At a mean follow-up of 3.4 years, the rates of all-cause mortality did not differ between patients who underwent PCI or CABG and, interestingly, the treatment effect was consistent irrespective of diabetic status and SYNTAX score.[8] Patients with a high SYNTAX score were relatively under-represented in pivotal RCTs comparing CABG with PCI for LM revascularization, precluding any definite conclusion with regard to the impact of CAD complexity for myocardial revascularization decision-making in patients with unprotected LM disease.

In this issue of the journal, Kahraman et al.[9] provide further real-life clinical outcome data on 60 patients (mean age: 60 years; male: 75%; diabetic: 46%) with chronic (30%) or acute (70%) coronary syndrome who underwent unprotected LM PCI with DES over an 8-year period at a high-volume, tertiary center in Turkey. The primary outcome measure of this retrospective, single-center, observational study was major adverse cardiac and cerebrovascular events (MACCEs), a composite of all-cause death, non-procedural myocardial infarction (MI), stroke, and ischemia-driven target vessel revascularization. A significant proportion of the patients had multivessel CAD and low-to-moderate CAD complexity (SYNTAX score of ≤32), while only 1 out of 4 patients presented with high anatomical complexity (SYNTAX score ≥33). Distal LM stenosis was treated in the majority of patients, but only 27% had true distal LM bifurcation. Accordingly, provisional stenting was the preferred approach in the majority of patients and a 2-stent strategy was performed in only 18% of patients. Importantly, post-dilatation to optimize stent implantation was performed in 82% of patients, but no intravascular imaging was used to guide PCI in addition to coronary angiography. At a median follow-up of 25 months, the primary composite endpoint was observed in 27% of patients who underwent LM PCI and was mainly driven by extremely high rates of all-cause death (17%), whereas non-procedural MI and stroke were observed in only 7% and 3% of patients, respectively. The rates of target vessel revascularization at a median follow-up of 2 years were surprisingly low in this LM PCI cohort (5%). Compared with patients who remained event-free during the follow-up period, patients with a MACCE had a greater bur-

den of comorbidities (higher SYNTAX score II PCI), higher CAD complexity (higher SYNTAX score), and greater residual obstructive CAD after LM PCI (higher MACCE residual SYNTAX score). Finally, the authors identified chronic kidney disease, the absence of post-dilatation, and the residual SYNTAX score as independent predictors of MACCE during follow-up.

Despite obvious significant limitations, including a non-randomized single-center study design, the small number of patients included, the lack of control group, the inclusion of non-atherosclerotic causes of LM disease, the lack of clear definition for non-procedural MI and the uncertainty concerning the adjudication of death causes, all of which might have biased the study conclusions, the analysis highlights some important issues concerning contemporary LM PCI that may inform decision-making for an optimal patient-centered treatment selection for LM revascularization.

First, the higher residual SYNTAX score observed in patients with a MACCE and the identification of residual SYNTAX score as an independent predictor of adverse outcomes add to existing knowledge that a greater extent of residual atherosclerotic disease after PCI is associated with poorer clinical outcomes. The residual SYNTAX score was found to be a strong predictor of 5-year mortality after PCI with DES in a post hoc analysis of the SYNTAX trial and these results were consistent in the subgroup of patients with LM disease. Importantly, both complete revascularization and a residual SYNTAX score of ≤8 yielded a comparable risk of 5-year mortality, whereas a residual SYNTAX score of >8 was associated with a 35% all-cause mortality rate at 5 years of follow-up.[10] These findings advocate for a paradigm shift from the historical perspective of LM revascularization alone to the need to achieve complete, or a reasonable level of incomplete revascularization in LM patients to further improve prognosis following LM PCI with DES and to reduce the current gap in outcomes with respect to CABG, despite the presence of multivessel or complex CAD in a significant proportion of patients.

Second, the mortality rates observed in the present study are surprisingly higher than those reported in contemporary LM PCI trials.[4,5] However, these findings should be interpreted with caution considering the lack of intravascular imaging guidance used for PCI optimization in this LM cohort. The negative impact of suboptimal stent optimization on clinical outcomes following LM PCI is further supported by the strong independent predictive value of the absence of stent post-dilatation on the occurrence of MACCE. LM PCI remains a technically challenging procedure, and safely achieving optimal procedural outcomes is essential, given that the implications of a suboptimal PCI result in patients with LM disease are more likely to affect survival than in any other anatomical subset. In addition to the importance of operator volume and experience, contemporary standards for unprotected LM PCI should include pre-procedural intravascular imaging for procedural planning, meticulous lesion preparation, stenting with the exclusive use of newer-generation DESs, proximal stent optimization with or without kissing balloon-inflation based on the bifurcation technique used, and post-procedural imaging with further optimization, when indicated. The use of intravascular ultrasound (IVUS) for LM PCI provides superior information compared with coronary angiography alone to guide the appropriate procedural techniques, such as the need for adjunctive or more aggressive lesion preparation, inform the choice of appropriate DES dimensions to achieve the largest minimum stent area, and optimize procedural results by maximizing stent expansion, reducing severe stent malapposition and avoiding geographic miss. These concepts have recently translated into 46% and 34% reductions in 30-day and 1-year mortality rates, respectively, among patients undergoing IVUS-guided LM PCI in a large-scale, real-world, nationwide registry.[11] Accordingly, the use of IVUS is currently advocated as a class IIa recommendation to optimize treatment of unprotected LM lesions.[7] The need for a more generalized adoption of intravascular imaging in LM PCI should not obscure the paramount importance of intracoronary physiological lesion guidance; additional PCI technical aspects, such as optimal distal LM bifurcation management; and the use of potent dual antiplatelet therapy, all of which are necessary to optimize LM PCI outcomes. A state-of-the-art PCI using the SYNTAX II strategy, which includes heart team decision-making based on a clinical tool combining both anatomical and clinical factors, coronary physiology-guided revascularization, newest-generation DES, IVUS-guided stent implantation, contemporary chronic total occlusion revascularization techniques, and guideline-directed medical therapy, was recently shown to provide superior clinical outcomes

at 1-year follow-up compared with the PCI arm of the original SYNTAX trial among patients with multivessel CAD.[12] Of note, an exploratory analysis suggests similar outcomes with respect to the composite endpoint of all-cause death, any MI, stroke, or repeat revascularization at 1 year between patients undergoing PCI using the SYNTAX II strategy and the historical CABG cohort of the SYNTAX trial.[12] These findings provide evidence of the potential impact of the latest technological refinements in the field of PCI to improve clinical outcomes among patients with complex CAD and may help inform the design of future, highly needed, RCTs comparing PCI and CABG in patients with LM disease. The use of the most contemporary PCI techniques, including intracoronary imaging and physiological guidance and optimization, coupled with refined patient selection and shared decision-making may certainly lead to a significant improvement in outcomes of LM patients treated with PCI and provide novel important insights in the current, highly emotional debate of the optimal revascularization strategy for patients with LM disease.

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