The conundrum of the treatment for left main coronary disease

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New data published in the last two years have made the process of making evidence-based therapeutic decisions regarding the optimal revascularization strategy in patients with left main coronary disease (LMD) increasingly challenging.

Often, the cardiovascular community turns to meta-analyses to address controversial topics. In an individual data pooled analysis of 11 randomized trials and more than 11,000 patients published in 2018, Head and colleagues found that in patients with multivessel disease or left main stenosis, the use of percutaneous coronary intervention (PCI) was associated with a significant increase in mortality at 5 years follow-up when compared to coronary artery bypass grafting (CABG) (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.06-1.37, p=0.004).[1] Mortality was similar between the interventions in patients with left main disease (10.7% after PCI *vs* 10.5% after CABG, HR 1.07, 95%CI 0.87-1.33, p=0.52), regardless of diabetes status and Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) score. The presence of LMD was not a significant effect modifier, providing no statistical support for the concept that the relationship between PCI and CABG is systematically different in the presence of LMD.[2]

The Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial randomized 1905 patients with LMD to CABG or PCI and published its 5-year results in 2019.[3] In EXCEL, there was no statistically significant difference in the primary composite outcome of death, myocardial infarction (MI) and stroke between the two treatment arms. The Society for Cardiovascular Angiography and Intervention (SCAI) definition of MI, that intrinsically favors PCI (due to the higher enzymatic release associated

with surgical manipulation after CABG), was approved by the Steering Committee and used as the main MI definition in the trial. The protocol pre-specified however that the MI rates would also be calculated using the more widely adopted Universal Definition of Myocardial Infarction.

In EXCEL, the rate of perioperative MI by the SCAI definition in the surgical arm was higher than in all the other major CABG vs PCI trials[4,5] and was mainly responsible for the neutral result of the trial (as the incidence of all non-perioperative events was higher in the PCI arm). To date, the MI results based on the Universal Definition have not been published in peer-reviewed journals, and the EXCEL trial has attracted considerable controversy.[6,7] An analysis of mortality at 5 years (arguably the most important outcome) found an excess risk in the PCI group (odds ratio 1.38, 95%CI 1.03-1.85).

A month later, the Nordic–Baltic–British Left Main Revascularisation (NOBLE) trial published its 5-year results.[8] NOBLE enrolled 1,201 patients with LMD who were randomized to CABG or PCI and its primary outcome was a composite of death, non-periprocedural MI, stroke and repeat revascularization. At 5 years, the primary outcome occurred significantly more frequently in the PCI arm (HR 1.58, 95%CI 1.24-2.01, p=0.0002). No significant excess of death in the percutaneous arm was noted (HR 1.08, 95% CI 0.74 to 1.59, p=0.70), although the number of deaths was small and the resulting confidence intervals were wide.

The publication of the two trials with apparently divergent results was accompanied by a fiery debate in the cardiovascular community, in particular with regard to the excess of deaths seen in EXCEL and not significantly so in NOBLE, and on the different definitions of MI used in the trials[6,7].

In this issue of the European Heart Journal, Ahmad et al present a trial-level meta-analysis of the five trials that compared CABG and PCI in patients with LMD.[9] At a mean weighted follow-up of 67 months, the authors found no difference in mortality, a higher rate of repeat revascularization and non-periprocedural MI in the PCI arm, and a higher rate of periprocedural MI in the surgical arm. This meta-analysis is an important contribution as it evaluates the totality of the randomized evidence addressing the question. There are, however, important limitations of pooling trials from very different eras and with major procedural and methodological differences (the increase in statistical precision come at the price of a decrease in clinical relevance).

So, what is the take home message from the Ahmad meta-analysis and the formidable analytic effort devoted to the definition of the recommended treatment for patients with LMD in recent years? Shall the clinician dealing with the decision to indicate CABG or PCI in a patient with LMD during the daily Heart Team discussion be concerned by the excess death seen in EXCEL or be reassured by the lack of significant difference in NOBLE and in Ahmad trial level meta-analysis? Is CABG associated with a higher or lower risk of MI and is perioperative MI different from spontaneous MI?

Even if confused by the apparently discordant results and unfamiliar with the subtle methodological differences probably responsible for them, every clinician is well aware of the different mechanisms of these two revascularization strategies,[10] and is equipped to weigh the risk:benefit equation for an individual patient. Currently, for patients with multivessel disease who are suitable for both CABG or PCI, the evidence is convincing that CABG is associated with

a lower risk of death and cardiac events in the longer term; based on the available data it does not seem that things are different for patients with left main stenosis. However, in patients for whom surgery presents an unreasonable risk or who are more interested in short-term outcomes, PCI is a very welcome alternative (**Figure 1**).

Thinking of the 50-year old single parent caring for their three children, the 75-year old retired veteran with lung cancer impatient to walk his daughter down the aisle next month, the professional airline pilot, or the busy businessman in the middle of a multimillion-dollar transition that really cannot wait, we all recognize the challenges of translating this evidence into clinical practice. The discrepant results of the trials may very well be the results of the fact that we are dealing with a heterogeneous group of patients- a few with isolated LMD versus those with LMD and multivessel disease, although there is currently no good evidence to support the concept of LMS as a discrete patient group with a different treatment effect. It is highly likely that one size does not fit all in clinical practice! CABG and PCI should not be seen as rivals but rather complementary strategies largely based on patient characteristics and preference, and methodologically appropriate interpretation of the research evidence. The key to the improvement in patients' outcome, as recommended, is the Heart Team discussion.[11]

The LMD controversy over the last few months highlights some key issues and responsibilities of physicians, trialists, professional societies and, the cardiovascular community in general. Trials should be designed to answer important clinical questions and have clinically relevant and, where possible, standardized outcomes. The analytic approach, as well as a minimum period of follow-up, should also be standardized. That is not to say that innovation is precluded.

Indeed, the protocol-described strategy of the EXCEL investigators to use their new MI definition, but in addition to publish the conventional Universal Definition of MI, was not without merit. But both MI outcomes should have been shared (or the protocol amended and an explanation made in the paper).

The involvement of industry is important but needs to be clearly defined, and, ideally, trials should be run and overseen by fully independent committees with appropriate transparency and checks and balances in place. Like in other fields of science, data should be made available to other investigators and be confirmed by independent groups not involved in the publication of the initial trials.

The key to improving the outcome of patients with LMD (as well as other cardiovascular and non-cardiovascular diseases) is the honest and transparent collaboration between all the parties involved. After so much controversy, let's start again working together in the best interest of our patients!

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Figure 1. Treatment algorithm to be considered by the Heart Team deciding between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). LMD: left-main disease; MVD: multi-vessel disease.