Editorial

Coronary revascularization strategies in patients with multivessel disease: is it all about diabetes?

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Coronary artery disease (CAD) is the worldwide leading cause of mortality, with increasingly prevalent manifestations due to population aging and growth (1). From an anatomic standpoint, CAD varies from atherosclerosis of a single major epicardial vessel to more advanced presentations with multiple vessels simultaneously involved. Numerous clinical trials have appraised the comparative efficacy and safety of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for multivessel CAD revascularization (2). In particular, SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) randomized patients with left main and/or three-vessel CAD (3), whereas BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) randomized patients with two- or three-vessel CAD (and was prematurely interrupted due to slow enrollment) (4). Both studies reported increased rates of combined ischemic events in multivessel CAD patients treated by PCI, driven by higher rates of repeat revascularization (3,4).

Repeat revascularization is a debated outcome in comparative studies of PCI and CABG, because it is typically carried out by PCI, with a minor impact on quality of life and prognosis compared with other harder clinical endpoints, including death or myocardial infarction (MI) (5). Indeed, in both SYNTAX and BEST, PCI and CABG did not differ with respect to death and MI in patients with multivessel CAD (3,4). This finding comes at variance with the results of FREEDOM (Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), another large-scale trial of PCI or CABG for multivessel CAD patients with diabetes mellitus (DM), where the 5-year rates of death and MI were significantly lower in the CABG group (6). Adding to statistical issues (SYNTAX and BEST were individually underpowered for detecting significant differences in death an MI), a simple explanation for the inconsistent results of SYNTAX and BEST on one side, and FREEDOM on the other side is the role of DM as a potential treatment effect modifier. If this were true, one may argue that the results of SYNTAX and BEST would have been different if patients with DM were excluded. This hypothesis was the object of a recent patient-level meta-analysis from Chang *et al*. published in the Journal of the *American College of Cardiology* (7). The authors pooled 1,275 non-DM patients with multivessel CAD from SYNTAX and BEST, and compared PCI and CABG in a "post-hoc" fashion. At a median follow-up of 5 years, they found CABG to reduce significantly the risk of death by 35% and the risk of MI by 60% (7).

When a new treatment significantly improves survival, we may confidently conclude that it should be preferred over the current standard. However, death is relatively infrequent in non high-risk patients and consequently a large number of patients must be randomized for a study to be adequately powered for this outcome. Meta-analyses may

overcome this limitation by pooling data from individual studies and thereby increasing the statistical power of the comparison between treatments. A patient-level meta-analysis holds some unique advantages over other types of meta-analysis (i.e., study-level and network): (I) first, it allows the calculation and reporting of time-to-event curves and statistics; (II) multivariate models can be used to adjust for eventual confounders between treatment groups; (III) comparisons can be conducted in subgroups of interest to explore and assess treatment interactions, if any. Indeed, the study by Chang *et al*. exhibits some of these advantages. However, some limitations should also be considered: (I) random treatment allocation is lost if subgroups of interest are not pre-specified and no stratified randomization is undertaken; (II) proper statistical methodologies are necessary to adjust for multiplicity in comparisons (i.e., Bonferroni's correction); (III) adequately powered studies should follow positive subgroup analyses to confirm their results, which should be intended only as explorative and hypothesis generating.

The finding of a significant reduction in mortality with CABG was somehow unexpected given the exclusion of patients with DM, and remarkable when looking at the constant separation of the survival curves. Multiple reasons may explain the long-term advantage of CABG over PCI even in non-DM patients. First, by bypassing the lesion, CABG offers protection against proximal atherosclerotic disease (8). There is also preliminary evidence suggesting protection against distal CAD progression in bypassed vessels, especially when arterial conduits are used (9). These disease-modifying effects may support better outcomes in patients with diffused CAD. In contrast, PCI treats the tightest lesion in a diffusely diseased segment without protection from proximal or distal CAD progression (8). In-stent restenosis and neo-atherosclerosis are additional limitations of PCI at long-term follow-up. Finally, completeness of revascularization, which is more likely to be achieved by CABG (10), has been associated with reduced rates of adverse ischemic events at follow-up (11). Beyond mortality, the pooled analysis of SYNTAX and BEST also highlighted an increased risk of MI with PCI. This finding cannot be overlooked, because MI was the primary cause of cardiac death in SYNTAX (12). Interestingly, the incidence of stroke, an expected shortcoming of CABG, did not differ across treatments. This finding should be put into perspective since current stroke preventive strategies such as the use of minimal or no-touch aortic techniques and adequate medical therapy after surgery might justify a decrease in the incidence of post-CABG stroke compared with the past (13).

Based on the analysis from Chang *et al*, should we ultimately discourage the use of PCI in all non-DM patients with multivessel CAD? Our short answer is no, consistent with the reflection that multivessel CAD may present very differently, i.e., with two simple lesions in as many coronary vessels or with diffuse disease and complex lesions in all three coronary vessels. In addition, the pooled analysis of SYNTAX and BEST suggests that the rates of death and MI achieved by PCI and CABG are comparable in the subgroup of patients with less angiographic complexity (7). This is in line with current guidelines recommendations that justify the use of PCI as an alternative to CABG in patients with low SYNTAX score (14). Heart Team discussion and patient's preference should be also factored in this kind of decision-making. In contrast to patients with no DM, the long-term benefit of CABG in those with DM appears to be independent from angiographic complexity in some studies (15,16) but not in others (17), which represents a call for future studies. Clearly, although some consequences of DM (i.e., diffuse disease, chronic kidney disease) are prognostically more important than just belonging to this category (18), there is still a need for improving the outcomes of PCI in this setting (i.e., with better stents, better drugs and functionally- rather than anatomically-guided procedures) to make it a more competitive strategy for patients with multivessel CAD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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