Interventional therapies in ischemic ventricular dysfunction: facts and versions!

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The treatment of patients with coronary artery disease (CAD) aims to reduce the risk of death, myocardial infarction, and ultimately to protect myocardial function, which is the major variable responsible for the prognosis of patients with CAD (1). Studies have clearly shown that patients with preserved ventricular function have a good prognosis irrespective of the number of diseased coronary vessels, but patients with systolic ventricular dysfunction have a poor prognosis, irrespective of the treatment applied (2). Although middle-aged patients with preserved systolic function have 1% to 3% overall mortality per year, patients with systolic ventricular impairment have about a 6% overall mortality in contemporary trials, with the best-evidence treatment being used (1).

The role of coronary revascularization to improve left ventricular (LV) function and reduce mortality has been investigated in several studies over the past few decades. The first historical study that compared CAD treatments was the CASS trial (2), which suggested that a few patients with 3-vessel disease with ejection fraction below 0.50 would have a survival benefit if they underwent revascularization with coronary artery bypass surgery (CABG) compared with medical therapy alone. The analyses from the CASS registry (3) of patients with CAD and severe ventricular impairment (ejection fraction ≤0.35) also have shown a survival benefit with CABG. Since the CASS results, although some retrospective studies have assessed this matter, major methodological limitations, especially concerning the indication for the procedures, have limited stronger conclusions. However, it is important to emphasize that this and other unmeasured confounders are inherent in observational studies.

Due to methodological difficulties, a long period passed until contemporary clinical trials emerged to reassess the efficacy of revascularization compared with medical therapy in patients with systolic ventricular dysfunction and CAD. More recently, three prospective randomized studies, the Heart Failure Revascularization (HEART) trial (4), the PET and Recovery following Revascularization (PARR-2) trial (5), and the Surgical Treatment for Ischemic Heart Disease (STICH) trial (1), have contested the value of revascularization or viability testing in patients with ischemic cardiomyopathy. The landmark STICH trial showed that medical therapy reached the same overall survival rates at 5-year follow-up, but lower rates at 10-year follow-up (1,6). However, although this is the best current evidence so far, its results should be carefully analyzed. One of the concerns about this study is the lack of information about myocardial ischemia, which might have resulted in the selection of patients with fibrotic myocardium or conversely viable but not ischemic myocardium, and this may have attenuated the possible higher benefits of myocardial surgical revascularization.

Assuming that revascularization of ischemic myocardium in patients with systolic ventricular dysfunction has the potential to restore the contractile function of stunned myocardium and improve survival (7), the comparison of revascularization strategies is of upmost importance. In the current era, and with the technological progress of coronary angioplasty and the development of drug-eluting stents, the rates of restenosis have diminished and thus short- to long-term results might be different from the results of previous studies with bare-metal or the older drug-eluting stents (8). On the other hand, although efficient revascularization may be achieved with percutaneous treatment with a less aggressive approach, the efficacy of angioplasty therapy in ischemic heart failure is uncertain and deserves to be assessed.

In this scenario, a recent study from Bangalore and colleagues (9) evaluated the benefits of percutaneous coronary intervention (PCI) in patients with severe ventricular dysfunction (ejection fraction ≤35%) and multivessel CAD compared with the most studied treatment, CABG, in the era of everolimus stents, a second generation eluting stent. To compare the efficacy of both therapies, the authors performed an observational study with 4,616 patients with double and triple-vessel CAD, excluding left main disease, from percutaneous and surgical registries from New York state hospitals. Because of the great disparity in baseline characteristics between both groups, the authors performed propensity score matching to balance both treatment groups, and thus, to assess the effectiveness of CAD revascularization strategies. However, major concerns about this analysis deserve to be highlighted. Before the matching, the surgical group comprised 3,265 patients (CABG), and the majority of patients had triple-vessel disease with proximal obstructive lesion of left descending coronary artery. After the matching, there was a significant change in this group, which became a majority of patients with double-vessel disease without a significant obstructive lesion in the left descending coronary artery and, thus, a less severe group. It is known that the superiority of surgical treatment compared with percutaneous treatment is related to the complexity of the anatomical lesions or to the number of coronary vessels diseased. Moreover, the angioplasty group maintained its pre-matching characteristics, which included mostly patients with double-vessel disease without lesion of the left descending coronary artery. Therefore, the selected post-matching groups favored the results of PCI treatment, because the patients had less severe coronary lesions and were free from left descending artery obstructions. Thus, extrapolation from the results of this matching cohort population of less severe patients cannot be generalized to all patients with multivessel CAD with systolic ventricular dysfunction.

It is noteworthy that the propensity score-matching tool may be capable of balancing the baseline characteristics between groups, but not all differences can be completely balanced. Moreover, the authors themselves recognize that this sophisticated tool may not include variables, such as frailty, that may have influenced the treatment choice.

Assuming that CABG is the most chosen treatment for patients with ischemic heart failure (10), the reason why patients undergo percutaneous treatment instead of surgery cannot be clarified in this retrospective analysis. In addition, non-measured confounding factors, such as the extension of coronary disease (diffuse or focal), the SYNTAX score, and comorbidities that could be assessed by surgical risk scores (STS or EuroSCORE), were not considered in this study. Furthermore, this retrospective study does not have information on viability and ischemic testing and angina. Over the past decades, studies showed that in the presence of viable myocardium, revascularization in patients with ischemic ventricular impairment leads to improvement in mortality as well as LV function in comparison with medical therapy alone (11,12). However, other studies, such as the STICH viability substudy (13), reported no difference in all-cause mortality regarding the presence of viability, after adjustment for the other baseline variables. This study, however, also has some limitations. Unfortunately, contemporary studies are very limited that compare the effectiveness of the various viability tests in improving outcomes after revascularization and, therefore, no testing modality can currently be considered the gold standard. It seems that not all viable myocardium recovers after revascularization and the probability of recovery and reverse remodeling is affected by several factors, including the timeliness, ischemia, completeness, and long-term patency of revascularization (14,15). Among patients with CAD, it is assumed that the presence of myocardial ischemia induced during stress testing may be associated with a worse prognosis and plays a role in the decision for myocardial revascularization. However, the evidence has emanated largely from studies in patients with normal or only mildly impaired LV systolic function (16). It is acceptable that the effects of revascularization, regardless of the type (CABG or PCI), are linked to the overall extent of ischemic myocardium, which might be identified by the presence of inducible myocardial ischemia on stress testing. Because of the numerous methodological limitations of studies with inducible ischemia stress testing and severe LV function, such as a STICH subanalysis (17), uncertainties persist regarding the role of coronary revascularization in patients with or without inducible ischemia. Angina has long played a central role in the management of patients with CAD and ischemic cardiomyopathy. The presence of angina has an important influence on the decision to perform coronary revascularization. Analysis of patients in the CASS registry (3) based on the predominance of angina versus heart failure symptoms revealed that those with angina as the predominant symptom and an ejection fraction ≤35% had better survival following CABG than patients with mostly heart failure symptoms. However, in

the STICH trial (18), stratified solely based on the presence or absence of angina, there was no difference in all-cause mortality in patients randomized to medical therapy alone. However, in this study, angina classification was not standardized across sites and relatively few of the patients studied had Canadian Cardiovascular Society class III/IV angina. In addition, patients without angina were more likely to have diabetes and had more viable myocardium.

Results from this study showed similarities between angioplasty and bypass surgery regarding death from any cause during a mean follow-up of 2.9 years. The interpretation of this information should also be looked at cautiously. The benefit of surgical treatment in myocardial revascularization studies became apparent after some years during follow-up, especially in patients with severe systolic dysfunction, because of the initial higher mortality rates associated with CABG (6). In an analysis from a subgroup of 651 patients with severe systolic dysfunction from the CASS registry (3), bypass surgery was associated with better survival rates after 5-year follow-up compared with medical therapy alone. However, this study was performed more than 30 years ago, in an era when medical therapy was quite different compared with the modern current therapy for heart failure and CAD. The most contemporary randomized trial in this scenario, the STICH trial, did not show a significant reduction in overall mortality for CABG compared with medical therapy after 5-year follow-up, although in the surgical group it showed a reduction in secondary study outcomes, such as cardiovascular mortality, and also a reduction in overall mortality in the "as treated" CABG group (1). Analysis of the data from 10-year follow-up of the STICH trial (6) showed a statistically significant reduction in overall mortality with CABG compared with medical therapy, thus, confirming the benefits of the surgical strategy in the long-term follow-up.

Other issues must be pointed out in this study, which weaken the results and its further conclusions. Many studies have shown that CABG achieves complete revascularization in a greater proportion of patients compared with PCI and suggest that the magnitude of clinical benefit is enhanced among patients in whom revascularization is complete (CR) versus incomplete (IR) (19). After the application of the propensity score-matching tool, the selected cohort of patients was composed of a great number of patients with incomplete revascularization (about 80%). Because most of these were patients with double-vessel disease, one can suppose that quite frequently the surgical group received a single arterial graft. Furthermore, patients from the angioplasty group who underwent incomplete revascularization had higher rates of myocardial infarction, complementing the current evidence that incomplete percutaneous treatment has a worse prognosis in comparative revascularization studies (20).

Studies comparing different strategies with contemporary techniques of surgical revascularization in patients with ischemic heart failure are fundamental to CAD treatment. However, these studies are scarce and most of them have many methodological concerns. Besides the limited evidence, many challenges cause the clinical decision to be difficult to make in daily practice. The understanding of the pathophysiology underlying this condition and the struggle to optimally revascularize ischemic and possibly hibernating myocardium to restore myocardial function is the final road in clinical evaluation. However, the interpretation of clinical variables as well as the diagnostic tools to better select the group of patients that have the greater potential benefit of interventional procedures is still not clear. Moreover, the comparative impact of different strategies of myocardial revascularization in this specific group of patients should be carefully addressed. PCI has been rapidly developing in recent years, with more flexible stents, biocompatible polymers and increasing use of endovascular imaging and functional assessment by fractional flow reserve, and the use of more potent antiplatelet agents. However, by its very nature, it is capable of only treating the coronary stenosis focally. In addition, concerns also remain about its effects on the microvascular function that may have an impact in patients with a low ejection fraction.

Individualization is essential is this context but some assumptions are fundamental. What would be the benefit of revascularization of scared tissues? Certainly none. On the other hand, what would be the benefit of revascularization to viable but not ischemic myocardium? Probably none. This should be the cornerstone of our thinking to better treat our patients with ischemic heart failure. The decision regarding the best treatment option has still not been clarified in the existing literature, in the way that a judicious clinical judgement is still warranted to treat such a challenging group of patients. So far, CABG seems to be the ongoing standard treatment in ischemic myocardium, although select patients with coronary lesions amenable to PCI, such as less complex 3-vessel CAD (SYNTAX score <22), or in the case of multiple comorbid patients, angioplasty might be an alternative option. Finally, medical therapy might also be a good option in those patients with mostly scared tissues or non-ischemic myocardium, in

which revascularization will probably not bring any further advantage over current best-evidence medical therapy. However, this question still needs to be tested in future clinical trials.

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Footnote

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Comment on: Bangalore S, Guo Y, Samadashvili Z, *et al.* Revascularization in Patients With Multivessel Coronary Artery Disease and Severe Left Ventricular Systolic Dysfunction: Everolimus-Eluting Stents Versus Coronary Artery Bypass Graft Surgery. Circulation 2016;133:2132-40.

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