Editorial

Chronic total occlusion: no more meta-analysis, please—a randomized clinical trial is urgently needed

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Percutaneous treatment of chronic total occlusions (CTO), defined as >3 months old, total obstruction of a coronary artery, is a phenomenon that has gained popularity in the portfolio of Cardiac Cath Lab Units, facilitated by the development of new technologies that allow addressing cases not feasible a few years ago. Despite its growing popularity, these are procedures that require a highly experienced operator, long sessions with increasing radiation dose to the patient and operator, and the risk of potentially serious complications. It is therefore very important to know the risk-benefit balance that this technique can provide in a given patient. The recent meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome by Hoebers (1), offers new and interesting facts that force once more to ponder. In an extensive review of all studies published in the literature, Hoebers concluded that a successful percutaneous treatment of a CTO is associated with an improvement in the ejection fraction (EF) with an absolute increase of 4.44%, a reduction in the adverse remodeling and an improvement in survival (OR: 0.52). Without wanting to question the validity of this meta-analysis, the data provided by Hoebers also allows another interpretation. When the authors selected only studies in which there is a clear definition of the treated population, confirming that all patients have a CTO at least 3 months old and an evaluation period post procedure for more than 4 months, the average difference between pre and post procedure EF is 4.71 (95% CI: 3.26-6.16) in the successfully treated group of patients and 2.21 (95% CI: –1.46 to 5.89) in the technique failure group of patients. So, in both groups the EF increases very slightly (only in the first case being statistically significant) and the difference between the increases in EF in both groups is actually 2.5 points. Whether this way of analyzing a meta-analysis can be very questionable from a statistical point of view, what we have no doubt about is that this small difference, quite probably less than the coefficient of variation of many techniques that analyze the EF, is clinically very poor. Therefore, despite the conclusions of Hoebers's meta-analysis, we are not sure that percutaneous treatment of a CTO, associated with an improvement in the EF, can provide any clinical significance.

The second outcome of Hoebers's meta-analysis indicates that successfully revascularized patients have a better prognosis than patients without it. There is no doubt in this statement, but we question that this better outcome is due to the success of the procedure and not due to other confounding variables. In a review of 13 studies included in a previous meta-analysis by Joyal (2), many variables that are associated with the prognosis were not described in baseline studies, so there is a possibility that both groups compared (successfully and unsuccessfully revascularized patients) were different (3). In the absence of a control group (not revascularized patients), it's very difficult to know what the specific role of revascularization in these patients is.

In our point of view, in order to understand the role of revascularization in patients with CTO, at least these four important concepts, should be previously clarified.

First, it is unclear what is the impact of a CTO, in the prognosis of patients with chronic ischemic heart disease or after an ACS. For example, patients with CTO included in the Horizons study, had worse prognosis than patients without CTO (4). In this study, patients with CTO were older and had more hypertension, diabetes,

kidney failure, worse EF and Killip class, and had more history of myocardial infarction, angioplasty and bypass surgery. The authors conclude literally: "The present study is a post hoc analysis from a large randomized clinical trial of patients with STEMI undergoing primary PCI and is limited by its observational nature. There were numerous differences in baseline clinical, angiographic, and procedural characteristics between the groups, and although multivariable Cox's proportional hazards analysis was performed, residual unmeasured confounders cannot be excluded. As such, the results of the present analysis should be considered hypothesis-generating". The Horizons study is included in the recent meta-analysis in which O'Connor concludes that patients with acute myocardial infarction and a no culprit artery CTO have a worse prognosis than patients without CTO (5). Unfortunately, in this meta-analysis there is no reference to differentiate baseline characteristics of the patients in both groups, which could explain the difference in prognosis, regardless of the presence of a CTO. It is interesting to note the observational study of Ariza-Solé, in which the presence of a CTO in patients with STEMI treated with primary angioplasty loses the prognostic value when the COX regression model with all variables are included [HR of 2.79 (95% CI: 1.71-4.56), P=0.001 in univariate analysis and HR of 1.76 (95% CI: 0.85-3.75), P=0.166 in multivariate analysis] (6).

Secondly, in our opinion the role of myocardial ischemia in the absence of angina, as an indication for revascularization, is not fully clarified, which frequently occurs in patients with CTO treated percutaneously. The current indications for revascularization in the clinical practice guidelines have, in our opinion, a very weak scientific base (7). In the Courage study, angioplasty was associated with a greater reduction in the ischemic area, quantified exercise tests, compared to medical treatment (8), but angioplasty in patients with moderate to severe ischemia did not affect the prognosis of patients compared to medical treatment (9). In addition, a meta-analysis of studies that have evaluated the effect of ischemia treated with angioplasty, has concluded that there is no effect on mortality, reinfarction or angina at follow-up. It is important to be aware of the ISCHEMIA TRIAL trying to prove whether treatment of moderate to severe ischemia detected by imaging techniques benefit from revascularization, something currently unknown in our opinion (10).

Thirdly, it is very risky to conclude that the improvement in ventricular function after a revascularization technique, improves prognosis in patients with ventricular dysfunction. In this sense, the STICH study failed to prove benefit from a complete revascularization with coronary bypass surgery, in patients with ventricular dysfunction and multivessel disease (11). Surprisingly, in this study, this lack of benefit was not dependent on the existence of viable myocardial territory (12). It is important to emphasize this, because often myocardial viability is required, something that at the moment is very difficult to assess.

Finally, as noted earlier, there is a strong suspicion that patients with CTO successfully treated are substantially different from patients in which the technique fails. This suspicion is supported by the fact that, when all prognostic variables are included in the multivariate analysis, the success in treating a CTO has no longer impact in the prognosis. This hypothesis is what has been reported by two major Japanese groups with experience in the treatment of CTO. In the series of CREDO-Kyoto registry cohort-2, including 1,524 patients, Yamamoto described in the multivariate analysis that the success in treating a CTO has no impact in reducing mortality or reinfarction (13). In the series of the National Cardiovascular Center in Osaka (Japan), which includes a total of 820 patients, the analysis adjusted for confounding variables concludes that there is no benefit in the treatment of chronic occlusions compared to medical treatment (14).

So, waiting for ongoing randomized studies, seems prudent at the present time, that only symptomatic patients (angina despite optimal medical treatment) are treated in order to improve them (15). In the absence of any symptoms, other indications to improve prognosis (ischemia, viability, etc.) should be carefully evaluated.

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Footnote

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