IJC Heart & Vasculature 33 (2021) 100761

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Editorial

Prognostic impact of left ventricular function in patients with acute myocardial infarction and concomitant chronic total occlusions

Conquering chronic total occlusions (CTO) remains the last frontier for percutaneous coronary interventions (PCI) [1–3]. These complex procedures remain associated with lower success and higher complication rates than PCI of on non-CTO vessels. CTO PCI requires longer interventions, a larger amount of contrast media, higher radiation exposure, and also have a higher cost [1–3]. In the last decade major technical advances and novel therapeutic strategies (namely the retrograde approach) together with a growing operator experience, significantly improved the success rate of these procedures [1–3]. Nevertheless, CTO PCI remains uniquely challenging interventions and, therefore, in most centers are only performed by selected, highly experienced, dedicated operators [1–3]. On the other hand, the prognostic benefit of CTO PCI is still not well-established and, in fact, remains a matter of intense controversy [4–6]. In selected patients, successful CTO PCI has been associated with an improvement in symptoms and quality of life and also with improvements in left ventricular ejection fraction (LVEF) [4–6]. However, the impact of CTO PCI on hard clinical events (i.e., death and myocardial infarction) remains unsettled [4–6].

Accordingly, novel information on the prognostic impact of CTO in different clinical scenarios and on the potential clinical benefit of successful CTO recanalization is more than welcome to inform revascularization decisions in everyday clinical practice.

Present study

In this issue of the Journal Ito et al. [7] present an interesting study from Japan including 2,060 consecutive patients with acute myocardial infarction (AMI) undergoing primary PCI that were sub-classified according to: 1) LVEF and 2) presence of concomitant non infarct-related artery (non-IRA) CTO. Most patients had preserved LVEF (mean LVEF 56 ± 12%) and 8.3% of them had a concurrent non-IRA CTO. In patients with reduced LVEF (LVEF < 50%; 1/3 of patients), those with concurrent CTO had higher rates of 1-year all-cause mortality (34.3% vs 20.3%, $p = 0.001$) and major adverse cardiac events (MACE) (39.6% vs 19.6%, $p < 0.001$), compared with patients without CTO. However, in patients with preserved LVEF, results were similar in patients with and without concurrent CTO. Interestingly, non-IRA CTO was an independent predictor of all-cause mortality and MACE in the reduced LVEF group but not in patients with preserved LVEF. In addition, successful CTO recanalization was associated with an improved prognosis only in patients with reduced LVEF that, eventually, achieved a long-term prognosis similar to their counterparts without CTO. Overall, these results strongly suggest that in patients with AMI the prognostic impact of non-IRA CTO differs depending on baseline LVEF.

An important unresolved clinical question is whether and when staged recanalization of concurrent non-IRA CTO should be attempted in patients with AMI [1–6]. Only in patients with reduced LVEF? In those without a previous history of AMI in the CTO territory? In those with preserved wall motion (or demonstrable viability) in the myocardial territory subtended by the CTO? In those with objective evidence of CTO-related myocardial ischemia? In any patient with AMI and a non-IRA CTO? These issues remain unmet clinical needs. Hopefully, discussing some methodological issues concerning the current study [7] will shed some light on these burning questions.

First, this study stems from the large Japanese Mie ACS prospective registry involving 15 centers. Therefore, this appears to correspond to a largely unselected patient population, representative of AMI patients in real-world clinical practice.

Second, reassuringly, strict definitions were used. Non-IRA CTO was defined as complete obstruction of the non-IRA with TIMI 0–1 with an estimated duration of > 3 months or presence of collateral flow with Rentrop grade ≥ 1. Notably, only CTO in vessels ≥ 2 mm in diameter were analyzed as only these vessels may have a meaningful prognostic implication.

Third, in the reduced LVEF group, patients with CTO had significantly poorer baseline characteristics that may help to explain their adverse prognosis. In addition, of the 106 patients with CTO, 37 underwent successful staged CTO PCI, but 67 had not attempted (61) or failed [6] procedures. The same situation occurred in the group with normal LVEF. This is a critical methodological issue as the reasons for not attempting CTO recanalization may influence the study results. The absence of clear criteria and lack of data in this regard remains a matter of concern. Thus, it is important to recognize that despite careful efforts to adjust for unbalanced baseline characteristics many unknown confounders are likely to play a role in the decision-making process involved in the attempt of CTO recanalization. Likewise, the sub-analysis on the benefit of successful CTO recanalization in relation to LVEF is prone to selection bias and is only based on a small number of patients. Therefore, these results should be considered as hypothesis-generating and require confirmation in future studies.

Fourth, timing to non-IRA CTO PCI attempt is important in patients with AMI. In patients with reduced LVEF, there was a non-significant trend for a better outcome when recanalization attempts were performed > 1 month after the index AMI. However,

https://doi.org/10.1016/j.ijcha.2021.100761

these results are difficult to interpret because these patients also had more benign baseline characteristics. Besides, in this study, LVEF was evaluated with transthoracic echocardiography mostly within a week (median 5 days) after the index AMI. However, current knowledge suggests that the recovery of LVEF may take a longer time (up to 3 months after AMI). It is possible that a delayed evaluation of LVEF may have yielded different results and, perhaps, a lower number of patients with reduced LVEF. Whether a delayed evaluation of LVEF (potentially allowing for the recovery of stunned or hibernated myocardium), would have altered the results of this study remains unknown.

Fifth, when the Kaplan-Meier curves depicting the results of the study are critically scrutinized, a similar mortality pattern associated with the presence of non-IRA CTO appears to be present in patients with and without reduced LVEF. In fact, the lack of a statistical difference in mortality between patients with and without concurrent CTO and preserved LVEF may be explained by the better overall prognosis of this cohort and the smaller number of patients with non-IRA CTO.

Sixth, the lack of information regarding ischemia or myocardial viability before CTO-PCI is not aligned with current recommendations [1–3]. This study was unable to provide data on the extent of myocardial viability and of ischemic burden. Revascularization of non-viable myocardium has never been proved to be of clinical value. Likewise, the presence and grade of collateral circulation, that has been associated with a better prognosis in terms of contractile function after the CTO-PCI, was not evaluated in the present study.

Finally, this study only evaluated mortality during a relatively short period. Symptomatic status, quality of life, and potential improvement in LVEF, that remain important surrogated clinical endpoints after CTO recanalization, were not evaluated.

Previous studies:

Several randomized clinical trials have been performed to assess the role of CTO recanalization in selected patients [4–6]. However, most of them have been prematurely interrupted due to slow recruitment [4–6]. In patients with stable angina (n = 396), the EUROCTO randomized trial demonstrated a clear benefit of CTO PCI with regard to angina and quality of life (primary endpoint) as compared with optimal medical therapy alone [5]. The occurrence of MACE, however, was similar in both arms. The DECISION-CTO trial randomized 834 patients with at least 1 CTO, to CTO recanalization or not [6]. The primary end-point at 4 years (composite of death, AMI, stroke and any revascularization) was similar (22%) in the 2 arms. Changes in health status were also similar in both groups that experienced a significant but comparable improvement from baseline. However, the results of this trial are difficult to interpret as one-half of the patients in both arms underwent PCI of additional non-CTO lesions [6].

It is well established that LVEF remains a major determinant of prognosis after AMI. In addition, the prognostic relevance of the presence of non-IRA CTO in patients with AMI is also well-recognized [8–10]. Nevertheless, the value of non-IRA CTO recanalization in these patients remains highly controversial. In the EXPLORE trial [4] 150 AMI patients were randomly assigned to early CTO PCI and 154 patients were assigned to conservative treatment without CTO PCI. Primary outcomes, including LVEF and left ventricular end diastolic volume on cardiac magnetic resonance imaging at 4 months, were similar in the 2 arms. However, the subgroup of patients with CTO PCI at the left anterior descending coronary artery significantly improved their LVEF [4]. In a sub-analysis of this trial, Elias et al. [11] demonstrated that patients undergoing CTO PCI, as compared with those without CTO PCI, experienced a greater recovery of regional systolic function in the CTO territory, especially in the dysfunctional but viable segments on cardiovascular magnetic resonance.

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However, there is very limited information on the prognostic relationship between non-IRA CTO and baseline LVEF in patients with AMI. Mizuguchi et al. [12] sought to assess whether the presence of CTO contributes to a worse prognosis in patients with preserved LVEF after primary PCI. In this retrospective study, clinical outcomes of 353 consecutive patients with AMI and LVEF > 40% were compared according to the presence (n = 25) or absence (n = 328) of non-IRA CTO. LVEF and peak creatinine-kinase values were similar in both groups. However, 30-day mortality was significantly higher in patients with concurrent CTO (12% versus 0.9%; p < 0.001). Only 15 of the patients with associated CTO (60%) underwent recanalization attempts during hospitalization, but the potential benefit of these interventions was not reported.

Final remarks:

Altogether these findings suggest that patients with AMI and concomitant non-IRA CTO are at 'double jeopardy' [7], potentially leading to larger myocardial ischemia and necrosis, poorer LVEF and, eventually, higher short and long-term mortality. Importantly, the study of Ito et al. [7] further suggests a beneficial prognostic effect of CTO PCI in AMI patients with reduced LVEF. An intriguing question is whether current results suggest that CTO PCI attempts are not justified in patients with AMI and preserved LVEF. Paradoxically, however, one might anticipate that the amount of residual ischemia / viability would be larger in these patients. Accordingly, we believe that this information should not be used to disregard CTO PCI attempts in selected patients with preserved LVEF because some of them may have a large amount of ischemic myocardium to benefit from revascularization. The presence of viable myocardium and the amount of ischemic myocardium remain important factors to consider CTO PCI. These factors, together with the anatomic characteristics of the CTO, should be carefully evaluated and discussed in each patient on an individual basis. The results of this study should not be used to deny the potential benefit of non-IRA CTO in patients with AMI and preserve LVEF whenever this procedure is considered as clinically indicated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Received 5 March 2021
Accepted 9 March 2021