

Meta-analyses and randomized trials investigating percutaneous coronary intervention of chronic total occlusions: what is left to explore?

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The field of percutaneous coronary intervention of coronary chronic total occlusions (CTO PCI) is highly dynamic. This is mainly illustrated by the large number of technical advances that have propelled success rates of CTO PCI from 60–70% to as high as >90% in recent (selected) case series (1). However, the rationale for performing CTO PCI is currently largely based on observational data and untested hypotheses. Observational studies have suggested a reduction in the need for coronary artery bypass graft surgery (CABG), a reduced incidence of ventricular arrhythmias, and even reduced mortality after successful CTO PCI (2–6). Further hypothesis-generating research was recently published by our group in the form of a meta-analysis of observational studies investigating the evolution of left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) after CTO PCI (7). This study indicated a significant increase in LVEF of 4.44% [95% confidence interval (CI): 3.52–5.35%, $P<0.01$] after successful CTO PCI at a follow-up duration ranging from 1 to 36 months in 34 studies which included a total of 2,243 patients. Moreover, LVEDV was reduced by 6.14 mL/m² in a meta-analysis of eight studies comprising 412 patients that evaluated LVEDV after successful CTO PCI.

The results of our study were discussed in two editorial comment articles by Dr. Christakopoulos *et al.* and Dr. Boukhris *et al.* (8,9). The editorial by Dr. Christakopoulos and colleagues raised an important argument about the presumed importance of viability testing to guide the decision to perform CTO PCI aimed at improving LVEF. Prior research has shown that the extent of scar tissue

transmurality can reliably and reproducibly be assessed using cardiovascular magnetic resonance imaging (CMR) using late enhancement with a gadolinium-based contrast agent (10). Currently, a threshold of 75% transmurality is accepted to discriminate between viable and non-viable myocardium. This value was derived from a cohort of 21 patients undergoing CTO PCI who underwent contrast-enhanced CMR before the index procedure and at 5-month and 3-year follow-up (11). Regional myocardial function, measured as segmental wall thickening (SWT), improved in segments with a transmural extent of infarction (TEI) of <75%, and was unchanged in patients with TEI ≥75%. A study of 50 consecutive patients with a CTO who underwent contrast enhanced CMR showed that 32 patients (64%) had inducible ischemia and myocardial viability within the CTO territory (12). These 32 patients underwent a second CMR at 3 months after CTO PCI. An improvement in LVEF (63%±13% to 67%±12%, $P<0.0001$) and improvement in LVEDV (65±38 to 56±38 mL, $P<0.001$) was reported. This recent study elegantly illustrates the importance of adequate patient selection for CTO PCI using state-of-the-art imaging techniques.

The editorial by Boukhris *et al.* pointed out that our meta-analysis also showed a small, non-significant increase in LVEF in patients with failed CTO PCI procedures (improvement of 2.21%, 95% CI: –1.46 to 5.89, $P=0.24$) and interestingly, a slight deterioration in LVEF in patients with successful CTO PCI with re-occlusion (–0.15%, 95% CI: –3.14% to 2.83%, $P=0.92$). The authors of the editorial pointed out that this may be a result of the loss of collateral circulation which leads to myocardial infarction in case of

re-occlusion after CTO PCI (8). However, these studies were performed before the widespread uptake of drug-eluting stents. The incidence of restenosis and reocclusion, even in CTO lesions has significantly declined with current-generation drug-eluting stents (13). Therefore, this does not seem to be an important concern in the current era.

An important concern raised in both editorial articles remains the (relative) lack of availability of data from randomized controlled trials in the field of CTO PCI. Two randomized trials are currently enrolling patients. EURO-CTO trial (NCT01760083) which evaluates quality of life in patients undergoing CTO PCI compared with optimal medical therapy at 12-month follow-up and clinical endpoints at 3-year follow-up. The DECISION-CTO trial (NCT01078051) evaluating cardiac mortality and myocardial infarction up to 5-year follow-up in patients randomized to optimal medical therapy or CTO PCI.

The results of the first randomized controlled trial in the field of CTO-PCI were recently presented at the 2015 annual TCT meeting in San Francisco (14). In EXPLORE, 304 patients undergoing primary PCI for acute ST-elevation myocardial infarction (STEMI) and with a concurrent CTO in a non-infarct related artery were randomized to additional CTO PCI within 1 week after the index procedure or no additional CTO PCI. All patients underwent contrast enhanced CMR after 4 months to determine the primary endpoints of LVEF and LVEDV. At 4-month follow-up no difference was observed in terms of LVEF (CTO PCI $44.1\% \pm 12.2\%$ *vs.* no CTO PCI $44.8\% \pm 11.9\%$, $P=0.60$) or LVEDV (CTO PCI 215.6 ± 62.5 mL *vs.* no CTO PCI 212.8 ± 60.3 mL, $P=0.70$). Rates of major adverse cardiovascular events, a composite of cardiac death, myocardial infarction, and CABG were low in both groups (5.4% *vs.* 2.6% , $P=0.25$). A significant interaction was observed between CTO location and randomized treatment allocation in terms of LVEF at 4 months; in patients with a CTO located in the left anterior descending (LAD) coronary artery a significant improvement in LVEF was observed in patients undergoing CTO PCI *vs.* patients not undergoing CTO PCI ($47.2\% \pm 12.3\%$ *vs.* $40.4\% \pm 11.9\%$, $P=0.02$).

The EXPLORE trial is an important first step towards a robust body of evidence concerning clinical outcomes after CTO-PCI. Nonetheless, as of now many questions remain unanswered. The results from EXPLORE warrant further investigation into additional CTO-PCI in STEMI patients with a concurrent CTO located in the LAD. Moreover, the data from EXPLORE suggest that early PCI of a CTO

located in the RCA or the RCX is not beneficial in STEMI patients with a concurrent CTO. Because EXPLORE only included patients post-STEMI, future studies investigating clinical outcomes after CTO PCI in other settings are direly needed. The results from the EURO-CTO and DECISION-CTO studies are eagerly anticipated to shed further light on the safety and efficacy of CTO PCI in patients with stable coronary artery disease. And even when these two ongoing trials will be published, the answers to many clinical questions regarding CTO PCI will remain to be explored.

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Footnote

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

Response to: Boukhris M, Elhadj ZI, Galassi AR. Chronic total improvement in ventricular function and survival. J Thorac Dis 2015;7:E222-5.

Christakopoulos GE, Tarar MN, Brilakis ES, *et al.* The impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcomes. J Thorac Dis 2015;7:1107-10.

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