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# Reconsidering the evidence for CTO PCI: the devil is in the detail

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Over the last two decades, there has been an explosion in the number of percutaneous chronic total occlusion (CTO) procedures performed worldwide, with high success rates and a greater emphasis on education and training[1]. Despite technological advancements and the implementation of revascularisation algorithms, it is important to note that the evidence base supporting CTO revascularisation remains limited, primarily consisting of observational data from dedicated registries with only a handful of unblinded randomised controlled trials[2–5].

In this issue of EuroIntervention, Werner et al present the 3-year safety endpoints from a trial to Evaluate the Utilization of Revascularization or Optimal medical therapy for the treatment of Chronic Total coronary Occlusions (EuroCTO)[3]. This multicentre, unblinded study randomised 396 patients 2:1 to CTO percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) or OMT alone. The initial procedural success rate was high at 83.1% and rose to 86.6% with subsequent procedures. Despite a crossover rate of 17.5% from the OMT alone group to revascularisation, there was no difference in the intention-to-treat analysis of the primary safety endpoint of cardiovascular mortality and non-fatal myocardial infarction (3.7% vs 6.2%; p=0.29). A difference − in favour of CTO PCI − was only seen when analysing the composite of mortality, non-fatal myocardial infarction, and ischaemia-driven target revascularisation (21.2% vs 11.0%; p=0.008). Unsurprisingly, this difference was primarily driven by a higher rate of target vessel revascularisation in the OMT alone group (16.8% vs 3.5%; p<0.001). This finding can, at least in part, be attributed to the "subtraction anxiety" phenomenon commonly seen in unblinded trials[6]. This phenomenon results in a potentially inflated number of unplanned revascularisation procedures triggered by the natural tendency of physicians, when performing unblinded symptom assessment, to be guided by the perception that a necessary treatment has been withheld from the control group. Further potential impacts of the unblinded trial design were seen in the improvement in physician-assessed angina and the lower number of antianginal medications in the CTO PCI group at 1 year. There is power in telling a patient that the problem is fixed. This leads to a larger placebo component of the overall treatment effect on angina. It is also inevitable that smaller quantities of medications are prescribed for symptom relief due to the perceived belief that they will no longer be necessary.

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We congratulate the authors for successfully completing the 3-year follow-up of an ambitious randomised trial of symptomatic patients with CTO, considering the significant complexities associated with recruitment in the presence of concomitant significant bystander disease, investigator hesitancy in enrolling highly symptomatic patients, the risk of crossover, and the necessity for high-volume specialist centres. Whilst EuroCTO attempted to address many of these challenges, slow recruitment meant that it fell short of achieving the 1,200 patients necessary for adequate statistical power for the primary efficacy endpoint analysis.

The results of the current study lead us to consider the indications for CTO PCI. While the success and safety of these procedures has undoubtedly improved in recent years, the average in-hospital complication rate remains at 3%, with high periprocedural myocardial infarction rates and considerable additional procedural costs[7]. The question of the prognostic value of CTO

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remains a subject of debate and is influenced by study design. While meta-analyses[8] have shown a mortality benefit associated with CTO PCI compared to OMT alone, this finding is driven by observational data and is not confirmed by the randomised controlled trials. More randomised controlled trials, of adequate sample size, are required to fully answer this question.

Given the paucity of data showing mortality and myocardial infarction benefit, current coronary revascularisation guidelines recommend CTO PCI primarily to improve symptoms and quality of life[9]. While the present study provides reassurance that the observed symptomatic benefit does not come at the expense of long-term safety, symptom assessment must be interpreted with caution.

Symptoms are, by their very nature, difficult to assess, with variability stemming from both the patient and healthcare professionals in the reporting and assessment of their character and severity. Additionally, the methods for assessing symptoms after an intervention in clinical practice may be more nuanced and patient-specific to those utilised in research. Addressing some of these issues is necessary to inform future guidelines and clinical practice. The adoption of more innovative, contemporary, and personalised methods of recording patient symptoms may help to improve the quality of the data. App-based solutions which record daily symptom frequency and severity could potentially yield high-quality, patient-specific data, particularly when incorporated with other metrics such as the burden of antianginal medications[10]. Such approaches may deliver a greater statistical power to detect differences in treatment effects and may address some of the issues associated with symptom data.

Importantly, the subjectivity of patient-reporting and physician assessment of symptoms makes them particularly prone to the influence of unblinded trial design and unblinded clinical practice. The impact of unblinded assessment and the potential for an exaggerated effect size can only be minimised by the input of a placebo control into a randomised trial design. The true physical effect of an intervention must be quantified once the size of the placebo component is known. Placebo-controlled trials of interventional procedures are rarely performed for a variety of reasons, including the inherent risk of exposing patients to a placebo procedure without any potential benefit and the concerns around trial feasibility and the fidelity of blinding. This is particularly true for CTO procedures which are long, have higher procedural risk and complex practicalities, such as additional vascular access sites. The ongoing ORBITA-CTO Pilot Study (ClinicalTrials.gov: NCT05142215) aims to shed light on the feasibility of conducting placebo-controlled trials in this patient population. Its results will provide the data needed to design a pivotal, multicentre, randomised, placebo-controlled trial of CTO PCI to thoroughly evaluate the impact on symptoms. For now, we would recommend that, while improved success and safety rates are welcome, the indications for CTO PCI must be carefully considered in the knowledge that more data from placebo-controlled trials are needed to truly inform practice.

## Conflict of interest statement

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