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Dilemmas in cardiology: when to recanalize a chronic total occlusion

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The decision whether or not to recanalize a chronic total occlusion (CTO) of a coronary artery is truly a dilemma for the cardiologist. The procedure is in fact complex, with a non-negligible rate of complications and with a probability of success lower than that of non-obstructive lesions. The analysis of the data available in the literature, with the significant discrepancy between the results of the randomized studies and the observational studies, does not currently allow conclusive statements on the role of the percutaneous coronary interventions in CTO. It is therefore essential to incorporate clinical, anatomical and procedural elements into the decision-making algorithm. While awaiting new randomized clinical trials of greater dimensions and better methodology, a careful selection of patients is certainly essential, limiting the procedure to those who are symptomatic or who have a high ischaemic burden and excluding those who have no evidence of vitality, without which it is not legitimate to expect any benefit from the intervention. Finally, the presence of the collateral circulation does not in itself appear to be an element that should have a significant decision-making role.

Chronic occlusion of a coronary artery [chronic total occlusion (CTO) according to the Anglo-Saxons] is a complete or almost complete occlusion of a coronary branch, which has occurred for at least 3 months. It is generally the consequence of an acute event that went unnoticed or untreated or of a slow process of luminal narrowing during which the recruitment of collateral circulation preserves the function of the myocardial region located downstream of the occlusion. The symptoms caused by CTOs are often different from the usual symptoms of non-obstructive disease. Typical angina is in fact less frequent than other forms of chest discomfort and especially dyspnoea, which is generally the prevalent disorder. Asthenia, fatigue, and depression are also common. Furthermore, due to the slow progression of the disease, patients often get used to living with their problem, gradually reducing, almost without awareness, their level of activity until they consider themselves asymptomatic or attributing the symptom to different conditions such as aging or poor training. The finding of CTO is relatively common, being observed in 15–20% of patients with coronary artery disease and even more frequently, 50%, in subjects previously undergoing coronary artery bypass graft.

Patients with CTO are generally older than those with non-obstructive coronary artery disease and with more comorbidities (diabetes, hypertension, smoking, dyslipidemia, peripheral arterial disease, previous infarction) and present, largely for these reasons, a worse prognosis. In the case of ST elevation myocardial infarction (STEMI), the concomitant presence of a CTO on a non-culprit artery (which occurs in ~10% of cases) worsens the prognosis both in the short term and long term, especially if the artery responsible for the infarction was supplying collaterals to the CTO. The native artery most frequently site of CTO is the right, followed by the anterior descending and, at a significant distance, by the circumflex. The presence of grafts, as mentioned, makes the presence of a CTO more frequent both on the native vessel (flow competition) and on the bypass. Given the relative frequency of CTO detection, treatment is quite rare. In fact, most patients are started on medical therapy and only a minority undergoes revascularization: surgical (patients with multivessel disease and/or multiple CTOs) or, more rarely, percutaneous. Only 5% of all angioplasties are in fact performed for the treatment of CTOs and only 15–35% of CTOs are treated percutaneously. This is probably explained by the technical difficulty of the procedures, by the perceived greater risk profile of the same and by the lack of clear evidence of the benefits of invasive treatment so far.

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The success rate

The success rate of CTO percutaneous recanalizations [CTO percutaneous coronary interventions (PCI)] has progressively increased over the years, both due to the improvement of the materials available and to the greater competence acquired by the operators and currently stands at around 85–90% in the best centres, and around 60–80% in the largest registers and, therefore, more indicative of the real world.[1] Some scores have been defined (J-CTO, ORA, PROGRESS-CTO, RECHARGE, Euro-CTO CASTLE) which, based on the anatomical parameters of the lesion and the patient's clinical parameters, allow to predict the success and risk percentages of the procedure, facilitating a more accurate planning of the same, a better information of the patient and, finally, allowing to select the more complex cases to be treated with the help of expert operators or directly in the centres specialized in the technique. Without going into specifics, different techniques are now available (antegrade, antegrade with dissection, retrograde) which must all be part of the technical background of the operators and which must be used individually or in combination with each other depending on the characteristics of each individual case. The more recently introduced retrograde technique has allowed a significant improvement in success rates but, due to its greater invasiveness, it is also inevitably burdened by a greater risk of complications. The probability of success of CTO PCI is lower than that of PCI for non-occlusive lesions, even if complex, as documented by a recent study by Azzalini *et al.*,[2] which showed percentages of 74 and 98%, respectively. PCI CTOs also had an increased risk of coronary perforations (3.5 vs. 2%, $P = 0.04$) and cardiac tamponade (0.8 vs. 0.1%, $P = 0.001$) in the study, with no significant differences in terms of major adverse cardiac events (MACE) (4.1 vs. 5%, $P = 0.4$) and mortality (1.2 vs. 1.5%, $P = 0.51$). Other studies have instead revealed that the rates of recanalization and complications are similar whether the CTO is located on a native vessel or within a previously implanted stent. On the other hand, the results of the revascularization of the grafts or even of the native vessels occluded after a failed bypass are more disappointing. In fact, it is not by chance that the presence of a previous graft is one of the factors included in some of the risk scores previously mentioned to indicate a less chance of success of the procedure. Procedural success is then likely influenced by the location of the lesion. In fact, some studies show that CTOs of the circumflex have a lower probability of procedural success, perhaps due to the greater tortuosity of this vessel and the lower presence of collaterals, so much so that, for example, the PROGRESS-CTO score inserts the occlusion of the circumflex as an independent predictor of procedural failure.

Finally, to optimize the success of CTO PCI, the aid of imaging techniques is desirable, which can improve the preparation of the procedure computed tomography (CT), the crossing of the lesion [CT, intra-vascular ultrasound (IVUS)], and the positioning of the stent IVUS.

The complications

In parallel with the improved success rate over the years, a reduction in the complications of the procedures has also been observed which today, in the most expert hands, are estimated to be around 3% overall, a rate that is still high and in any case higher than that of procedures on non-occluded vessels. The most frequent are constituted by: problems at the level of vascular accesses, more frequent in subjects pre-treated with PY12 inhibitors, coronary perforation, more common in the treatment of right coronary arteries, especially if with complex anatomy and subjected to an aggressive procedure, pericardial effusion and tamponade (the previous belief that the manipulation of the pericardium during a previous cardiac surgery is protective in this regard seems to be denied), occlusion of lateral branches, peri-procedural infarction, need for emergency coronary artery by-pass graft, stroke, renal damage, skin damage from radiation. The risk of death is variable in the various cases but never negligible and fluctuates on values slightly lower than 1%.

In summary, therefore, CTO angioplasty is generally technically feasible, with good success rates, although lower than procedures on non-occluded vessels, and with a non-negligible but still acceptable complication rate.

Is it worth?

The technical feasibility of the procedure, however, does not in itself justify its execution. As for any medical act, the indication must in fact arise from the careful evaluation of the cost–benefit ratio. The costs of unblocking the CTO are considerable, in fact they are complex procedures, organizationally onerous for the structures due to the long time required, economically expensive and, last but not least, not free from risks, it follows, therefore, that also the expected benefits must be proportionate. The literature at the moment is not unequivocal in this regard, with discordant results especially between randomized and observational studies, with the former having provided results lower than expected and the latter, however subject to possible enrolment bias, instead much more positive. Much has been debated about the reasons for the results of the randomized studies and certainly the small number of patients enrolled, the high crossover rates between treatment arms, the short duration of the follow-ups, the poor selection of patients included, the mixing in the same subjects of treatment of CTOs and non-occlusive lesions, the inclusion of low-risk and paucisymptomatic patients, the non-homogeneous search for ischaemia and vitality prior to treatment have affected the quality of these studies, reducing their reliability. Observational studies, including many important registers, have instead provided, albeit with some dissonant voices, much more favourable results for the percutaneous treatment of CTO. These studies often benefit from the strength conferred by the large number of subjects observed and the long duration (even more than 10 years) of the analysis, which shows[3] how the benefits of the procedure (reduction of both total and cardiac mortality, of the risk of heart attack and subsequent revascularizations) become evident only after about 3 years from the operation, i.e. beyond the study periods of the randomized trials, to then progressively increase. However, registries and observational studies discount the arbitrariness of the selection of treated patients who are generally younger and 'healthier' than those

managed conservatively. Furthermore, the comparison is often not between revascularization and medical therapy but between a procedure crowned with success or failure, neglecting the possibility that the failure of the procedure itself could be the cause of a negative clinical outcome or that the failed recanalization is secondary to the greater complexity of the clinical or anatomical aspects of the patient and that it is this aspect and not the outcome of the procedure itself that negatively influences the prognosis.

The randomized trials

In the last decade, six randomized studies have been conducted on the subject: EXPLORE, REVASC, EURO-CTO, IMPACTOR-CTO, DECISION-CTO, and COMET-CTO for a total of 1892 patients. Each study was different from the others.

EXPLORE trial[4]: 304 patients with STEMI and CTO of a non-culprit artery, randomized to CTO PCI or optimal medical therapy (OMT), 4 months follow-up, 77% success, no difference between the two groups in terms of evolution of ejection fraction (EF) and end-diastolic volume (IDV) of the left ventricle, except for patients with CTO of the anterior descending artery who benefited from reopening.

REVASC[5]: 205 subjects with stable coronary artery disease randomized to CTO PCI or OMT followed up for 12 months; 89% procedural success. At the end of this period, no differences were observed in relation to the primary end point [wall thickening assessed with magnetic resonance imaging (MRI) in the area served by the CTO] or to the secondary end point, which evaluated the function indices of the left ventricle. Instead, there was a significant reduction in MACE, thanks to the reduction in the need for subsequent interventions.

EURO-CTO[6]: 396 symptomatic patients and with at least one CTO, randomized to CTO PCI and OMT vs. OMT; 87% success. At 12 months, no differences in MACE (secondary end point) but CTO PCI induced a significant improvement in the quality of life and angina frequency (primary end points). It should be noted that in the trial all non-obstructive coronary lesions were treated before randomization, the patients were symptomatic and in case of regional myocardial dysfunctions the demonstration of viability was required.

IMPACTOR-CTO[7]: 72 isolated right coronary CTO randomized to CTO PCI and OMT vs. OMT, procedural success 83%, 12 months follow-up. Significant reduction of the primary end point of myocardial ischaemia (assessed by pharmacological stress MRI with adenosine) after revascularization, improvement of the 6 min walking test and quality of life (secondary end points), no differences in MACE.

DECISION-CTO[8]: The largest study, with 815 patients with silent ischaemia, stable angina, or acute coronary syndrome (without STEMI) randomized to CTO PCI and OMT vs. OMT, 91% procedural success. At the end of the 4-year follow-up, no significant differences were observed in the primary end point including total death, heart attack, stroke, or revascularization. It should be noted that ~20% of subjects in the medical therapy group still underwent PCI, that any additional significant non-obstructive lesions were revascularized after randomization, that enrolment was slower than expected and was discontinued before reaching the initially estimated number of patients, that the preliminary search for myocardial viability was not among the inclusion criteria and that, lastly, most of the patients were poorly symptomatic.

COMET-CTO[9]: 100 patients with stable angina and/or ischaemia and/or vitality in the akinetic segments in the CTO territory, randomized to CTO PCI and OMT vs. OMT; 94% procedural success. In the PCI group, a significant improvement in the quality of life (primary end point) was observed in the absence of changes in the secondary end point evaluating MACE (non-fatal infarction, need for subsequent revascularization) and total mortality.

The apparent discordance of the results of these trials mainly depends on their different designs. Indeed, when the methodology was rigorous: symptomatic patients, with evidence of residual viability, additional non-CTO lesions treated prior to randomization, low cross-over rate between groups, a significant effect of CTO PCI was observed at least on the symptoms and quality of life. However, when the studies were conducted in a different way, the results were disappointing. The lack of effect of revascularization on hard end points undoubtedly remains but this may perhaps depend, based on the already mentioned observational studies, on the excessive brevity of the follow-ups and the modest number of patients enrolled. In a nutshell, therefore, from the analysis of randomized trials it emerges that CTO PCI is able to reduce the symptoms and improve the quality of life with at least a neutral effect on prognostic outcomes. It is obvious that in times of evidence-based medicine, further randomized studies, free from the previously exposed limitations, are necessary to definitively establish the usefulness of these procedures.

Possible benefits of chronic total occlusion percutaneous coronary interventions

Effects of chronic total occlusion percutaneous coronary interventions on total mortality

A recent meta-analysis[10] comparing CTO PCI and OMT shows that, of the 14 studies reporting total mortality data, only two show an advantage conferred by OMT, while the other 12 show an advantage by PCI. Pooling the data shows that medically treated CTO patients have a significantly higher risk of death than those revascularized [relative risk (RR) 1.99, $P = 0.0002$]. However, as mentioned, there is disagreement between observational and randomized studies; in fact, the observational ones significantly favour PCI (RR 2.09, $P = 0.0003$), while in the randomized the improvement in mortality is not significant (RR 1.41, $P = 0.27$). However, it should be noted that none of the randomized studies was specifically designed to evaluate the effect of the procedure on mortality.

Effects of chronic total occlusion percutaneous coronary interventions on cardiac mortality

The same meta-analysis[10] investigated the effects of CTO PCI on cardiac mortality. Eleven out of 17 studies reported the relative data and 10 of these showed an advantage in

favour of interventional therapy. Overall, medically treated CTO patients had a significantly higher risk of death than those revascularized (RR 2.36, $P < 0.00001$). Again the disagreement between observational and randomized studies is confirmed, with a significantly positive effect of CTO PCI in the former (RR 2.42, $P < 0.00001$) and no difference in the latter (RR 1.57, $P = 0.27$).

Effects of chronic total occlusion percutaneous coronary interventions on major adverse cardiac events

Ten studies among those included in Li's meta-analysis[10] considered MACE. In the overall analysis, the use of PCI reduced the risk of MACE compared to medical therapy (RR 1.25, $P = 0.03$), in this case with no substantial differences between observational (RR 1.25, $P = 0.0004$) and randomized (RR 1.38, $P = 0.33$).

Effects of chronic total occlusion percutaneous coronary interventions on heart attack risk

Also in the same meta-analysis,[10] 10 studies analysed the risk of heart attack. Three showed data favourable to medical therapy and overall OMT was not associated with a significantly increased risk of heart attack compared with CTO PCI (RR 1.65, $P = 0.06$). Again there was a disparity between observational studies, in which a significant increase in the risk of heart attack was observed without PCI (RR 2.04, $P = 0.002$) and randomized ones, in which there was a non-significant advantage of OMT (RR 0.73, $P = 0.21$).

Effects of chronic total occlusion percutaneous coronary interventions on symptoms

The results of the randomized trials (EURO-CTO, IMPACTOR-CTO, COMET-CTO) unanimously demonstrate the efficacy of PCI CTP in reducing the symptoms and improving the quality of life. The only discordant result, that of the DECISION-CTO, is too affected by the previously described methodological limitations (patients with little symptoms, non-obstructive lesions revascularized after randomization, absence of myocardial viability research) to contradict the outcome of the other studies. In the selection of patients to undergo CTO PCI, it would be intuitively useful to be able to predict the subjects with the greatest symptomatic benefit from the procedure. To this end, a score (OPEN-AP)[11] has recently been proposed which, by combining seven clinical variables (frequency of angina, frequency of use of nitroglycerine, presence of dyspnoea when walking with others, number of antianginal drugs, presence of multiple CTO, indication to the procedure for symptoms or not, result of the Patient Health Questionnaire-8), seems to be able to predict the effect of PCI on symptomatic improvement. However, the message underlying the score is, in a nutshell, that the patients who benefit most from CTO PCI are the most symptomatic ones together with those with depression.

Effects of chronic total occlusion percutaneous coronary interventions on ventricular function

There is also conflicting data on this aspect. In a meta-analysis[12] of 34 studies, it emerges that CTO PCI induces an improvement in EF of 4.44% ($P < 0.01$) and a reduction of IDV of the left ventricle of 6.14 mL/m^2 ($P < 0.01$). However, the only randomized study conducted on the subject, the aforementioned EXPLORE Trial,[4] did not show an improvement in left ventricular function except in the subgroup of patients with left anterior descending (LAD) CTO. A different effect depending on the vessel treated was also observed in the study by Choi *et al.*[13] in which a significant increase in left ventricular EF was observed only with treatment of the LAD and circumflex, but not of the right.

Effects of chronic total occlusion percutaneous coronary interventions on arrhythmic and sudden death risk

Patients with CTO appear to have an increased risk of arrhythmia and sudden death (SD), especially if the occlusion is of an artery causing infarction. A meta-analysis[14] considered six studies analysing the relationship between the presence of CTO and the occurrence of ventricular tachycardia (VT)/ventricular fibrillation or appropriate defibrillator therapy and found that occlusion was associated with a 1.68-fold increase in such events arrhythmics (RR 1.68, $P < 0.05$), above all, as already mentioned, if the CTO was in the vessel responsible for an infarction. The risk of VT recurrence after ablation is also higher in the presence of a CTO. However, it is not yet clear whether unblocking can reduce this risk and no randomized study has specifically examined this question. The only available data derived from an observational study[15] on 1162 patients undergoing CTO PCI which compared the incidence of SD and sustained ventricular arrhythmias between those in whom the procedure was successful and those in which it was unsuccessful. In the former, at the end of the 12-year observation period, a significant reduction (7.5 vs. 2.5% $P < 0.001$) of arrhythmic events was observed which, however, was entirely due to the subgroup with CTO in the artery responsible for heart attack. Conversely, in subjects with CTO of an artery not responsible for necrosis, revascularization, or not of CTO did not influence the subsequent arrhythmic risk (2 vs. 4% $P = 0.198$).

Diabetic and elderly patients

Approximately 40% of patients with at least one CTO have diabetes, and diabetes is considered a risk factor for developing a CTO. CTO PCI in these patients is more complex, resulting in a lower success rate, probably because the vessels have more calcium, are smaller in diameter, there is more endothelial dysfunction, and there is a higher atherosclerotic burden. The few specific data on the subject, always observational, apparently confirm the benefit of revascularization compared to medical therapy, with the superiority, however, of cardiac surgery.[16]

Compared to younger subjects, patients over 75 years of age have a lower success rate of PCI CTO, a higher MACE rate and higher short- and long-term mortality,[17] as is

the case easy to understand in light of their higher basis risk. However, comparing the outcome of those in whom the procedure is successful and of those in whom it fails, reiterating the limitations already expressed on a comparison of this type, some observational studies however show, even in the elderly, a positive effect on mortality due to work of the revascularization of the CTO.

Effect of chronic total occlusion percutaneous coronary interventions based on the artery site of the occlusion

Probably the site of the lesion does not influence the effect of the procedure but the available results are, once again, conflicting. In the aforementioned EXPLORE Trial,[4] the treatment of LAD coronary artery induced an improvement in EF after STEMI unlike what happened with the right and circumflex arteries. Also in the study by Yoneda *et al.*[18] and in the one already mentioned by Park *et al.*,[3] only the treatment of the CTO on the LAD improved mortality and not that on the right and circumflex arteries. In Gong *et al.*'s report,[19] on the other hand, there was no difference in the occurrence of MACE based on the artery treated as well as in the Canadian registry[20] in which no differences emerged in survival depending on the site of the lesion. On the contrary finally, in the aforementioned study by Choi *et al.*,[13] only the treatment of the right and circumflex, and not of the LAD, reduced the combined end point of total death and infarction.

Role of collaterals

Patients with CTO often present (80–90% of cases) an omo- and/or heterocoronary collateral circulation. If this is well developed, it generally allows maintaining myocardial viability but is often insufficient to ensure adequate blood flow outside resting conditions. Based on data extrapolated from patients with non-occlusive lesions, the presence of collateral circulation is perceived as protective against future adverse events. For this reason, patients with CTO and collateral circulation are generally referred to medical therapy alone for fear of procedural complications. In reality, an observational study[21] on 738 patients with CTO and good collateral circulation has instead shown that, compared to medical therapy, revascularization (in this case both percutaneous and surgical) significantly reduces the risk of death, both total and cardiac, and of MACE. The presence of collaterals, therefore, should not in itself be considered sufficient to discourage revascularization of the CTO.

Diagnostic workout

In the presence of a patient with CTO, in order to evaluate the indication or otherwise for an unblocking procedure, it is essential to research the presence of symptoms and evaluate their extent, taking into account their frequent atypicality. In the absence of disturbances, the presence and extent of ischaemia induced by the occlusion must be determined. In the event of normal or only slightly altered contractility (hypokinesia) of the segments downstream of the CTO, it is possible to assume with reasonable certainty the existence of vitality, without the need to seek it instrumentally, which instead becomes indispensable in the presence of akinesia. The choice of the method to be preferred for the research of ischaemia or vitality (single photon emission tomography, positron emission tomography, magnetic resonance, echo-dobutamine) depends on local availability and experience even if the magnetic resonance would seem to be preferred.

Conclusions

The decision whether or not to re-canalize a CTO is truly a dilemma for the cardiologist. The procedure is in fact complex, with a non-negligible rate of complications and with a probability of success lower than that of non-obstructive lesions. The analysis of the data available in the literature, with the significant discrepancy between the results of the randomized studies and the observational studies, does not currently allow conclusive statements on the role of the PCI CTO. It is essential to incorporate the clinical (symptoms, age, left ventricular function, comorbidities, presence and extent of ischaemia, and vitality), anatomical (complexity of the lesion, probability of success, and risk of complications), and procedural elements (experience of the centre and the operator) into the decision algorithm.

While waiting for new larger randomized clinical trials and better methodology, a careful selection of patients is certainly essential, limiting the procedure to those who are symptomatic or have (in analogy with what was considered for patients with non-occlusive coronary artery disease) a high ischaemic burden (the COURAGE nuclear sub-study suggests a mortality benefit in stable coronary artery disease when ischaemia affects more than 10% of the entire myocardial mass) and excluding those who have no demonstration of viability, in the absence of which it is not logical to expect benefit from the intervention. The presence of the collateral circulation does not in itself appear to be an element that should have a significant decision-making role. Finally, even the site of the lesion is not able to direct the use or otherwise of interventional treatment; however, even with all the uncertainty evident in the literature, the occlusion of the LAD can, most of the times, tip the balance towards the recanalization.

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