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Percutaneous Coronary Interventions for Chronic Total Occlusions: More Benefit for the Patient or for the Interventionist's Ego?

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SUMMARY

During the last decade, the interest of interventionists' community in chronic total occlusions has exponentially grown determining a fast advancement in dedicated equipment and techniques, which has resulted in high rates of procedural success and low rates of complications. However, in absence of randomized trials, the real benefit for patients remains not yet an unwavering evidence for all cardiologists.

ABSTRACT

Chronic total occlusions (CTOs) represent a common lesions' subset observed in patients undergoing coronary angiography. During the last decade, the interest of interventionists' community in CTOs has exponentially grown determining a fast advancement in dedicated equipment and techniques, which has resulted in high rates of procedural success and low rates of complications. Although different observational studies showed that CTO revascularization was associated with good clinical outcome, its real benefit for patients remains not yet an unwavering evidence for all cardiologists, particularly in absence of randomized trials. In addition, as compared to non-CTO lesions, the American and European guidelines downgraded percutaneous coronary intervention (PCI) in the setting of CTOs.

In the current viewpoint, we tried to identify patients who would take more benefits from CTO recanalization, and discussed the issues which might improve the appropriateness of CTO PCI.

Since 1985, Andreas Grüntzig identified the presence of chronic total occlusions (CTOs) as one of the major reasons for referring patients to the surgeon instead of treating them by percutaneous coronary intervention (PCI) [1].

The prevalence of CTOs in patients undergoing coronary angiography varies from 18% to 52% [2-4]. During the last decade, the interest of interventionists' community in CTOs has exponentially grown determining a fast advancement in dedicated equipment and techniques [5-7], which has resulted in high rates of procedural success and low rates of complications [8-10]. Although different observational studies showed that CTO revascularization was associated with an improvement of left ventricular ejection fraction [11-13], an increase in electrical stability [14] and a reduction of left ventricular remodeling [15], its real benefit for patients remains not yet an unwavering evidence for all cardiologists.

The Italian Registry of Chronic Total Occlusion (IRCTO) enrolled 1777 patients with at least one CTO, among 15,619 patients who underwent coronary angiography in 12 high-volume Italian centres during 1-year period; the overall prevalence of CTOs was 12.3% [16]. Notably, more than 2/3 of CTO patients had a multivessel coronary artery disease, and multiple CTO lesions (≥2) affected more than 10% of cases. Differently from the Canadian Multicenter CTO registry where less than 10% of cases underwent CTO PCI [2], 43,7% of patients enrolled in the IRCTO were attempted percutaneously, while the remaining patients were managed conservatively or referred for CABG (46.5% and 9.8%, respectively) [16].

Among patients enrolled in the European Registry of Coronary Total Occlusion (ERCTO), Galassi et al. [8] reported that in 63.3% of cases, electrocardiogram (ECG) did not show Q-waves with a normal ventricular motion in CTO territory, suggesting the presence of viability. Similar findings were reported by Fefer et al. [2], where only one third of patients had electrocardiographic evidence of myocardial infarction (MI), and only 17% showed a significantly reduced left ventricular (LV) function. However, ECG and echocardiography might underestimate the frequency of MI in CTO territory. Indeed, in 170 consecutive patients affected by CTOs, Choi et al. [17] found evidence of previous MI in 25% of patients by ECG Q-waves and in 69% by regional wall motion abnormality, while late gadolinium enhancement in magnetic resonance imaging (MRI) was observed in 86% of patients.

Some CTO patients might have well developed either ipsi- or contraleral collaterals wrongly suggesting the presence of sufficient myocardial blood flow for the CTO territory. Although previous reports have shown that the presence of collateral circulation is associated with myocardium viability [18], only 5% of CTO patients would have a collateral flow able to preserve ventricular function [19,20]. Furthermore, Sachdeva et al. [21] demonstrated the presence of resting ischemia, documented by resting Pd/Pa <0.80 (Pd = pressure distal to the CTO, Pa = pressure proximal to the CTO) in 78% of CTO patients. This underlines the importance of attempting CTO revascularization, regardless of the degree of collateral supply. Hence, should we give into the temptation to attempt all CTO lesions? The answer is definitely no [22]. The following question seems to be more appropriate: which patient would take a real benefit from CTO recanalization?

The answer depends on three parameters: symptoms assessment, ischemia evaluation and viability demonstration.

In the FACTOR trial, Grantham and colleagues [23] employed Seattle Angina Questionnaire at baseline and at 1 month, in 125 patients who underwent CTO PCI. Successful CTO recanalization was associated with significant early improvements in symptoms, function, and quality of life only among symptomatic patients [23].

Hachamovitch and colleagues [24] described the linear relationship between ischemic burden and the combined endpoint of death and MI, among patients with coronary artery disease managed by medical therapy. In the setting of non-CTO lesions, Shaw et al. [25] demonstrated a relationship between residual ischemia and survival after enrollment in the COURAGE trial, regardless of the management strategy employed (PCI with or without optimal medical therapy), and that PCI was associated with clinically significant reduction in ischemic burden, as compared with medical therapy. Recently, Safley et al. [26] showed that ischemic burden was reduced following CTO PCI and this reduction was correlated with the improvement of outcome. ROC analysis showed a baseline 12.5% of ischemic burden as an optimal cut-off to identify patients most likely to have a significant decrease in ischemic burden post-PCI, while those with a baseline ischemic burden <6.25% were more likely to have ischemia worsening post-PCI [26]. These findings suggest that CTO revascularization is appropriate, even in absence of symptoms, in patients with a large ischemic territory subtended by the CTO artery. Moreover, we have already shown that patients with non revascularized CTO lesions and severe perfusion defect had worse prognosis than those with normal or almost normal myocardial scan [27].

Myocardial viability can be assessed by various imaging modalities such as dobutamine stress echocardiography, single-photon emission computed tomography nuclear scintigraphy, contrast-enhanced cardiac MRI, and positron emission tomography. Comparing conservative (medical) versus invasive (PCI) strategy, Gerber et al. [28] showed a better 3-year survival in PCI group only in presence of viability. Kirshbaum et al.[29] observed both early and late improvements in regional LV function in the CTO territory, when baseline infarction transmural extent was <75%. It was also shown that multiple MRI derived viability parameters better identified CTO patients who would benefit from PCI [30]. Conversely, 2 randomized controlled surgical trials, STICH (Surgical Treatment for Ischemic Heart Failure) and PARR-2 (PET and Recovery Following Revascularization Phase 2), using thallium scintigraphy and positron emission tomography respectively, failed to demonstrate any benefit of viability assessment on clinical outcomes following revascularization strategies [31,32]; however, these latter studies have been criticized for several methodological flaws.

Based on the previous arguments, our current approach can be summarized as follows: in symptomatic patients with preserved wall motion or hypokinesia in myocardium subtended by the CTO, revascularization is indicated without any further imaging test; in asymptomatic patients with normal wall motion or hypokinesia in the CTO territory, a myocardial ischemia imaging test is recommended to evaluate the ischemic burden; finally, in case of akinesia or dyskinesia, viability should be demonstrated regardless of symptoms, before indicating CTO revascularization.

There are 2 clinical scenarios involving CTO lesions: isolated CTO and the setting of multivessel disease.

In case of lone CTO, symptoms are generally atypical, and angina could be less prominent than shortness of breath [33]. On the other hand, the potential benefit of a successful PCI could be diminished by the loss of the protective effect of collaterals in case of stent thrombosis or restenosis. Therefore, a percutaneous attempt of a lone CTO lesion should be deferred until intensive medical therapy is proven to be inadequate to satisfactorily improve symptoms. Indeed, the appropriate use criteria (AUC) for coronary revascularization in case of single-vessel coronary artery disease, downgraded CTO revascularization in comparison with non CTO lesions, in some clinical settings (Table1) [34]. However, if revascularization is clinically indicated, PCI is generally the chosen management strategy for a lone CTO. Lesions with a low J-CTO score (≤ 1), can be attempted by “non CTO expert” interventionalists, for training purposes [35]; while those considered to be difficult (J-CTO score >1) should be preferably treated by CTO dedicated operators, as well as CTO lesions already unsuccessfully attempted, and those suitable for retrograde approach. Of note, CABG may be also considered when left anterior descending (LAD) represents the target CTO vessel.

The previous arguments probably do not apply to patients with multivessel coronary artery disease, in whom recanalization of a CTO lesion has a prognostic value [36]. Regarding revascularization modalities, similarly to non-CTO lesions, the AUC provide a rating of "appropriate" for CABG and "uncertain" for PCI (even "inappropriate" in case of left main involvement) in CTO patients with mutivessel disease [34]. If this latter option is indicated, patients should be referred to experienced CTO dedicated operators.

In our opinion, a CTO expert operator should have already performed >150 CTO PCIs and should attempt at least 50 procedures per year to maintain his skills. Notably, 100 retrograde procedures represent an appropriate cut-off for expertise in such an approach. Importantly, the learning curve for CTO PCI should be a deliberate, stepwise process including proctoring and continuing medical education conferences, with patient safety being the primary concern during skills advancement.

The last ESC guidelines assigned a class IIa (level of evidence B) to CTO PCI in "patients with expected ischemia reduction in a corresponding myocardial territory and/or angina relief" [37]. However, we should also look at the same ESC guidelines, in the section regarding the indications for revascularization in patients with stable angina or silent ischemia [37]. For symptoms, revascularization of any coronary stenosis >50%, in the presence of limiting angina or angina equivalent unresponsive to medical therapy, is assigned a class IA. Similarly for prognosis, in the presence of proximal LAD stenosis >50%, or multivessel disease with stenosis >50% and impaired LV function (ejection fraction <40%), revascularization is assigned a class IA [37]. Accordingly, being the "maximum" of stenosis (100%), we are entitled to ask the following question: does CTO revascularization also deserve a class I indication?

The increase in appropriateness of CTO recanalization passes through three issues. The first issue is the advance in CTO PCI. In 2008, the date of ERCTO creation, 1303 procedures were performed; while in the last 3 years, more than 2600 CTO lesions per year were attempted. With the growing experience, the angiographic success rate has increased from less than 80 % in 2008, to 87 % in 2013. Notably, this improvement of success has been associated with an increased difficulty of attempted lesions (actually 2/3 of patients had a J-CTO score >1) (Figure1). These findings are similar to those reported by both American and Japanese communities of CTO dedicated operators [35,36]. Although, some authors reported that patients undergoing CTO PCI are still experiencing higher rate of procedural complications, than those undergoing non-CTO angioplasties [38-40], others did not find significant difference regarding complications rate between the two settings [41]. Indeed, CTO PCI in experienced hands represents a safe procedure, and cases of procedural death remain exceptional. In addition, no difference in term of death related to the procedure was observed between antegrade and retrograde approaches, while coronary perforation and non

Q-wave myocardial infarction were more often associated with retrograde PCI [8,38,42]. However, the majority of data reported in literature was predominantly from experienced operators and dedicated centres; thus, the results might be difficult to be generalized to all interventionalists. Furthermore, the definition of post-procedural myocardial infarction varies between studies; hence, the rate of such a complication could be underestimated in studies using a definition based on creatine kinase levels, as compared to those using the universal definition with troponin.

The second issue is represented by the impact of CTO revascularization within the concept of health status, which includes angina, dyspnea, exercise tolerance, limitation of activities, medication burden, self-image, and social functioning. Recently, Safley et al.[43] demonstrated the non-inferiority of CTO PCI, as compared to non-CTO PCI, in improving symptoms, function, quality of life and dyspnea. Comparing the impact on quality of life of different initial management strategies of CTO patients, Wijeysundera et al. [44] showed that PCI significantly improved physical limitation, angina frequency and disease perception; whereas, optimal medical therapy failed in all these criteria.

The presence of a CTO is one of the strongest predictor of incomplete revascularization by both CABG and PCI [4,45]. The importance of achieving a complete revascularization and its impact on prognosis underlines the benefits of successful PCI on patients survival, as the third issue. Indeed, in a meta-analysis including 23 studies and 12,970 patients, Khan et al. [46] showed that successful CTO PCI was associated with better long term survival, as compared to failed procedures managed conservatively (relative risk of 0.54, 95% confidence interval (0.45-0.65), $p < 0.001$).

Nevertheless, people already convinced by the available evidence regarding the usefulness of CTO recanalization are still a minority. In this respect, the Euro-CTO trial (NCT01760083) was initially designed to include around 1200 CTO patients randomly assigned to optimal medical therapy or PCI performed by experienced European operators, with quality of life at 1-year as a primary efficacy endpoint and 3-year MACE occurrence as primary safety endpoints. The enrollment phase is expected to end in June 2015. The criteria of inclusion based on symptoms, ischemia in the territory supplied by CTO, and viability as documented by <50% of transmural late enhancement on cardiac magnetic resonance or normal resting perfusion scan, could provide an appropriate selection of CTO patients. The results of this latter study and those of DECISION-CTO (Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion)

(NCT01078051) trial are also expected to better understand the usefulness of CTO percutaneous revascularization in improving prognosis and quality of life.

Finally, attempting CTOs contributes to improve the interventionalist's skills, and gives to him a constant lesson of humility and respect for the lesion and for the patient. The CTO operator is able to better understand his limits; this fact makes him unbiased to consider CABG or conservative strategy in patients non suitable for PCI.

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FIGURES LEGEND

Figure 1. ERCTO (2008-2014): Angiographic success and lesions' difficulty (as assessed by J-CTO score).

Abbreviations. *ERCTO=European Registry of Chronic Total Occlusions*

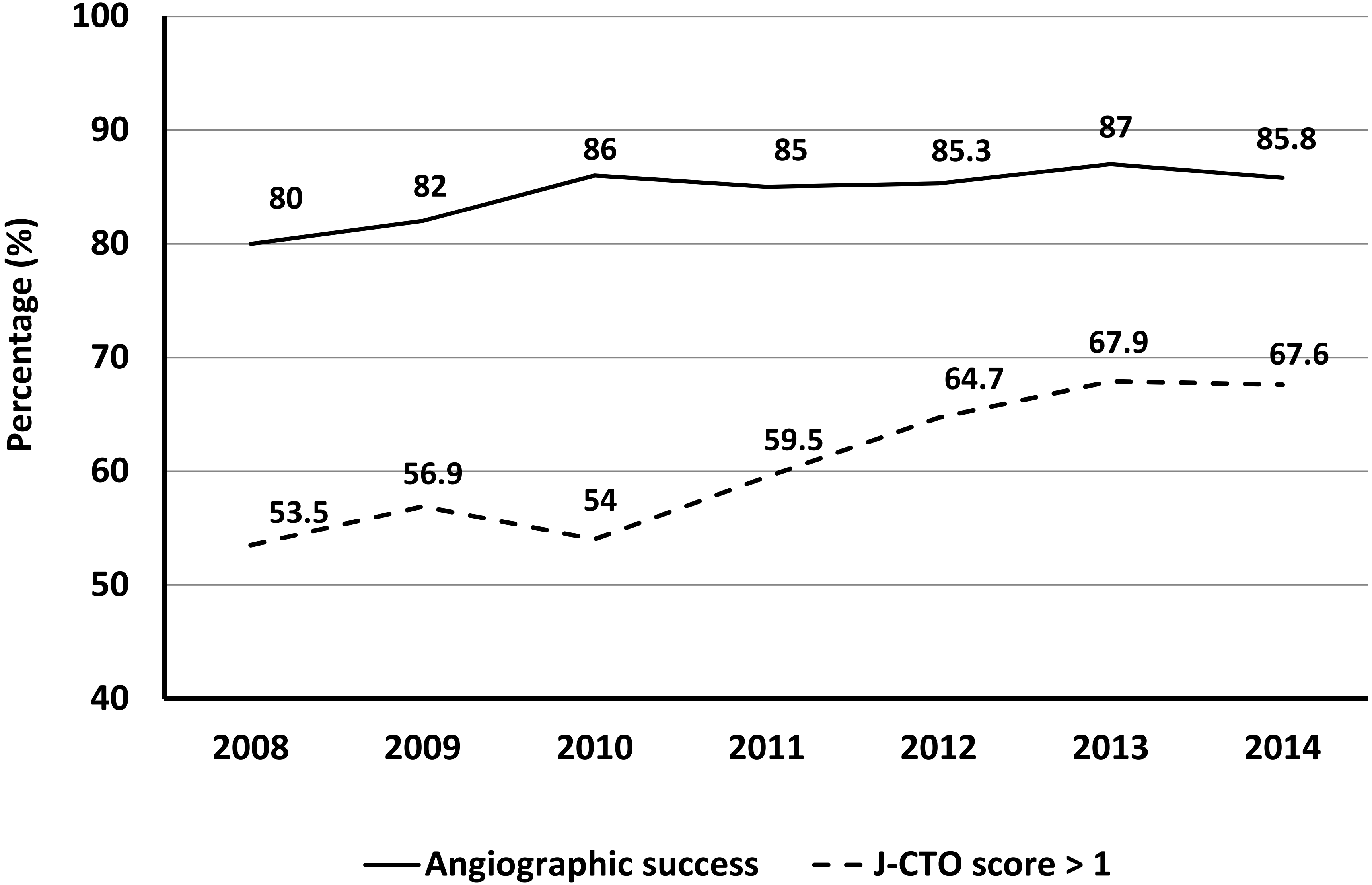
100
90
80
70
60
50
40
Percentage (%)
80
82
86
85
85.3
87
85.8
53.5
56.9
54
59.5
64.7
67.9
67.6
2008
2009
2010
2011
2012
2013
2014
Angiographic success
J-CTO score > 1

Table 1. Appropriate use ranking of CTO and non-CTO lesions in the patients with single-vessel disease

Symptoms on OMT	**Asymptomatic**			**Symptomatic Class I-II**			**Symptomatic Class III-IV**		
Risk based on non-invasive tests	**Low**	**Intermediate**	**High**	**Low**	**Intermediate**	**High**	**Low**	**Intermediate**	**High**
CTO lesions revascularization	*Inappropriate*	*Uncertain*	*Uncertain*	*Uncertain*	*Uncertain*	*Appropriate*	*Uncertain*	*Appropriate*	*Appropriate*
Non -CTO lesions revascularization	*Inappropriate*	*Uncertain*	*Appropriate*	*Uncertain*	*Appropriate*	*Appropriate*	*Appropriate*	*Appropriate*	*Appropriate*

Abbreviations.

CTO=chronic total occlusion; OMT=optimal medical therapy.

Interventional Cardiology

Should we give into temptation and attempt all chronic total occlusions?

"The decision-making process of whom to undergo chronic total occlusion percutaneous coronary intervention, should pass through a rational analysis, taking into account clinical and anatomical factors and operator's experience."

Keywords: chronic total occlusion • clinical indications • percutaneous coronary intervention

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Chronic total occlusion (CTO) is defined as the presence of thrombolysis in myocadial infarction (TIMI) flow 0 within an occluded coronary segment of greater than 3 months standing [1]. It represents a frequent coronary lesion subset encountered in everyday catheterization laboratory practice. Indeed, CTOs were present in 18% of patients with significant coronary artery disease and no prior coronary artery bypass graft [2], and Christofferson *et al.* [3] reported a CTO prevalence as high as 52% in a Veteran's Affairs population with significant coronary artery disease. Nowadays, clear evidence has been established regarding the benefits of CTO recanalization [4–6]. Although in the past decades coronary artery bypass graft was considered to be the gold standard for treating CTO lesions [3], recently, thanks to the significant improvements in equipment and techniques [7,8], CTO percutaneous coronary intervention (PCI) has become a more attractive and fashionable choice, as compared with surgery [2]. However, a question remains looking for an answer: should we give into temptation and attempt all CTO lesions in cath lab?

Proofs in literature

The decision-making process of whom to undergo CTO PCI, should pass through a rational analysis, taking into account clinical and anatomical factors and operator's experience. In fact, current guidelines [9] carry a Class IIa for CTO PCI in "patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise".

Symptom status, anti-ischemic medication, viability and ischemic burden are important factors which should be taken into consideration during the assessment of a patient candidate for a CTO revascularization. Indeed, Canadian Cardiovascular Society angina class >II, high-risk findings on non-invasive testing and/or optimal medical therapy in some combination are generally considered to be appropriate indications.

The key objectives of CTO recanalization include symptom relief (not only angina), increase in exercise capacity and improvement of quality of life. In a meta-analysis by Joyal *et al.* [10], patients with successful CTO recanalization had significant reduction in angina recurrency at 6-year follow-up, as compared with patients in whom the procedure failed (odds ratio 0.45). The FACTOR trial showed that procedural success was independently related to not only angina relief, but also improved physical function and enhanced quality of life as assessed by the Seattle Angina Questionnaire [11]. Notably, these reported benefits were only observed in symptomatic patients at baseline [11]. However, the low rate of anti-ischemic medication prescribed in the latter study (calcium channels inhibitors 13%, nitrates 38%, β-blockers 73%) could represent a bias favoring the difference observed between successfully and unsuccessfully recanalized patients [11]. Maximal anti-anginal medical therapy is defined as the use of at least two classes of therapies to reduce anginal symptoms [12]; for a CTO patient an assumption in anti-anginal medication prescription, according to patient tolerance,

Future Medicine part of fsg

could postpone the need for revascularization and even avoid it in some cases.

On the other hand, functional imaging tests are important tools, for making the decision to attempt or not a CTO. Indeed, CTO recanalization is indicated in the presence of objective evidence of viability/ischemia in the territory of the occluded artery of more than 10%, as shown by the current guidelines on myocardial revascularization [12]. In addition to scintigraphy prognostic value [13], the interest in cardiac MRI has increased in recent years. Baks *et al.* [14] correlated myocardial viability by cardiac MRI before and 5 months after PCI with improvements in left ventricular systolic function. Moreover, scar burden assessment by delayed-enhancement MRI was able to predict improvement in segmental wall thickening, particularly in those with <25% transmural extent of infarction (21 ± 15 to 35 ± 25%; $p < 0.001$) [15].

"The key objectives of chronic total occlusion recanalization include symptom relief (not only angina), increase in exercise capacity and improvement of quality of life."

The decision to revascularize a CTO lesion also passes through a careful analysis of anatomical features. Although right coronary artery is the most commonly involved vessel, Safley *et al.* [15] showed that 5-year survival rates were only significantly extended in the successful PCI of left anterior descending CTO (88.9 vs 80.2%; $p < 0.001$). In the presence of three-vessel disease and/or left main involvement (high SYNTAX score), surgical revascularization remains the reliable alternative able to ensure good outcome [12]. On the other hand, the presence of heavy calcifications, vessel tortuosity and collateral circulation may be important in determining not only who can benefit from recanalization but also the approach to adopt. In this respect, Morino *et al.* [16] described the so-called J-CTO for grading lesion difficulty; this latter was able to predict the probability of successful guidewire crossing within 30 min [16].

There is no doubt that operator's experience impacts on the outcome. Indeed, Thompson and colleagues [17] have shown a clear added value of high-operator CTO-specific case volume, particularly in retrograde approach, improving technical success of CTO PCI without adversely impacting patient outcomes. However, experience should never mean unwisdom.

Conclusion

In conclusion, despite the recent advances in techniques and equipment and the importance of a complete revascularization [18], the answer of the title question is definitely no, even for experienced operators. Indeed, the decision making process for PCI of a CTO lesion should pass through a rational and wise balance between the expected benefits and the procedural risk. Moreover, we should not forget that optimal medical therapy and surgery still belong to the therapeutic armamentarium for CTO patients.

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