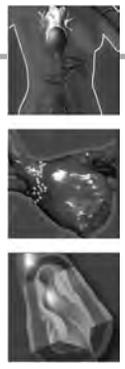

Outcomes following successful recanalization of chronic total coronary occlusions

A chronically occluded coronary lesion is observed in approximately 20–30% of patients in whom the diagnosis of coronary artery disease is established by coronary angiography. By contrast, a chronic total coronary occlusion (CTO) as a target of a percutaneous coronary intervention (PCI) constitutes less than 10% of the PCI volume in current practice. This discrepancy is explained in part by the specific technical challenges posed by a CTO with a low primary success rate, and a high lesion recurrence rate. The latter is addressed by the use of drug-eluting stents, and the former is improved considerably with recent technical advancements and specialization of operators. There are three principal indications to revascularize a CTO, which are the relief of clinical symptoms, the improvement of impaired left ventricular function, and a potential improvement in survival. Despite the absence of a randomized clinical comparison between conservative and interventional treatment of CTOs, numerous nonrandomized studies support the beneficial effect of PCI for CTOs.

KEYWORDS: chronic total coronary occlusion ▪ coronary artery disease ▪ percutaneous coronary intervention ▪ prognosis ▪ stable angina pectoris

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Chronic total coronary occlusions are a unique type of coronary lesions

This article aims to highlight the controversial issues regarding the indication for treatment of chronic total coronary occlusions (CTOs), and summarizes the historic and most recent data on clinical outcome in light of current interventional guidelines.

The assessment of the available data on the treatment and outcome of CTOs requires a uniform definition of the term 'chronic coronary occlusion'. A variety of definitions influenced the perception of the lesion morphology and long-term outcome [1,2]. In order to find a common ground for future discussion of technique and patient outcome, a consensus was recently published by a group of European experts, suggesting a firm definition of CTOs as those with a documented duration of occlusion of at least 3 months with absolutely no flow through the lesion (Thrombolysis In Myocardial Infarction 0 flow) [3]. Occlusions within 1–3 months duration can be addressed as recent occlusions, and within a period of 4 weeks after an acute myocardial infarction (MI), as subacute occlusions. These subacute occlusions were the target of the only randomized trial on the prognostic impact of revascularizing an occluded artery [4,5], but some have mistakenly extrapolated the results of this trial to include revascularization of CTOs [6].

Besides the duration of the occlusion, a prior history of MI in the territory of the occluded artery also influences the outcomes assessment. We are dealing with two different clinical settings when we look at the group of patients with an occluded artery. One is the group targeted in a subacute stage by the Occluded Artery Trial (OAT) [4] with a prior history of ST-elevation MI (STEMI) not being treated acutely by primary percutaneous coronary intervention (PCI), and the other is the group of patients in whom a CTO has developed with enough collateral supply to prevent MI, and who often display perfectly normal regional left ventricular (LV) function at rest. In the former group when the occluded artery was not opened early, collaterals will still develop and may save myocardial cells in the border zone of the infarct [7], and a revascularization may still be warranted depending on the proof of a clinical benefit derived from such an intervention.

Prevalence of CTOs

Data on the prevalence of CTOs among patients with coronary artery disease vary considerably between 20–30% depending on the setting in which the prevalence is assessed [8–10], but in contemporary clinical practice the number of CTOs make up 6–10% of the PCI volume [11–13]. They represent a unique set of lesions with regard to the complexity of the required interventional

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technique, but also with regard to the discordant view on the indication to treat these lesions. In general, patients with a CTO present with stable angina pectoris except if other coronary lesions progress and lead to unstable angina. They are at particularly high risk if the collateral supplying artery is involved in an acute MI as the territory at risk is increased [14,15].

This article will summarize the clinical evidence currently available regarding the indication to revascularize CTOs, based on three basic goals to improve the outcome in any patient with stable angina pectoris:

- To relieve exercise-limiting symptoms of angina or dyspnea, similar to the indication in stable angina caused by nonocclusive lesions; due to the chronicity of their lesion, patients have often downgraded their personal exercise threshold and may even appear mildly symptomatic, but objective measures of ischemia prove significant ischemia in 95% of collateralized CTOs [16];
- To improve regional LV dysfunction in the territory of the occluded artery, provided there is residual viability; the latter can nowadays be readily assessed by MRI with late contrast enhancement [17];
- To improve the prognosis, especially in patients with multivessel disease.

If the CTO procedure fails in a coronary artery with a large supply territory, the patient should be referred to coronary artery bypass graft (CABG) for complete revascularization [18].

Is it time to reconsider the indication for PCI in CTOs?

In the early guidelines, the presence of a CTO was considered a contraindication for PCI and it has gradually achieved a higher status of acceptance, but remains in category II of the guideline recommendations [19,20]. The reason for this situation were the two major setbacks in treating a chronically occluded artery: a low primary success rate to open the artery and the high risk of lesion recurrence and reocclusion after an initial successful recanalization. The high recurrence rate had been improved considerably with the advent of drug-eluting stents to levels similar to nonocclusive lesions [21–24], finally proven by randomized trials [25–27]. In addition, the problem of a low success rate had been dramatically overcome. Major improvements had been the introduction of specific guidewires, the adaptation of new wire techniques such as the use of two or more parallel wires [28–33], and the additional use of the transcollateral approach [34]. The latter led to a rapid development of new techniques such as the controlled antegrade and retrograde subinitimal tracking (CART) and reverse CART technique [35], and thus a considerable further increase in technical success rates [36–38]. Further improvements may come through the development of new adjunctive devices to aid in the most common mode of technical failure, when the wire takes a subintimal pathway and needs to be redirected into the true lumen [39].

Relief of symptoms after successful recanalization of a CTO

The treatment of coronary artery disease by revascularization has a primary effect on the relief of symptoms of angina, and thus the improvement of quality of life (QoL). The early randomized trial for surgical revascularization consolidated this observation with only a few subgroups that showed a survival advantage over a conservative approach [40,41]. Also for PCI, symptom relief is the primary objective. Careful selection of patients is required to balance the clinical benefit with the potential risk of periprocedural complications [42].

Randomized data to support the benefit of recanalizing a CTO with regard to symptom relief are not available. In a recent meta-analysis of trials comparing successful and unsuccessful procedures, the impact on clinical symptoms of angina was analyzed [43]. In six trials in which recurrence of angina was reported, this event occurred approximately 50% more often after an unsuccessful as compared with a successful procedure [44–49]. This meta-analysis compared 1030 successful with 570 unsuccessful procedures; the success rate in these studies was well below 70% as they originated from a period before advanced recanalization techniques had been introduced, and also before drug-eluting stents were used to help prevent lesion recurrence. Lesion recurrence, and together with this recurrence of symptoms, was a considerable factor in the era of balloon angioplasty and bare metal stent treatment of CTOs [21,50,51].

The problem with symptoms related to a CTO is their often atypical presentation. Unlike in patients with nonoccluded lesions, there is a baseline collateral blood supply to the myocardial territory distal to the occlusion, which is fully developed after approximately 3 months of occlusion duration [7]. Frequently patients with a CTO without a prior MI will have preformed

interarterial connections that alleviate symptoms of angina [52]. Furthermore, the chronicity of the situation may lead patients to adapt to their limited exercise capacity and not report this limitation as an acute symptom.

The effect of a successful revascularization was recently assessed by instruments of QoL evaluation in the FACTOR trial [53]. The authors observed an improvement of QoL after successful PCI, which was most pronounced in patients with a symptomatic state before PCI, whereas the improvement was less evident in asymptomatic patients. In fact, many of the patients with a CTO are considered patients with silent ischemia. Despite the observation that collaterals will have prevented regional dysfunction and MI in many of these patients, the functional capacity of the collateral system to increase myocardial blood supply during exercise is limited [54,55]. The fractional flow reserve assessed distal to an occluded artery is typically in the range below 0.5 [16], which clearly indicates myocardial ischemia [56,57]. As there is a considerable amount of data supporting the revascularization of coronary lesions causing silent ischemia of more than 10% of myocardial volume [58–60], as reflected in the recent guidelines on myocardial revascularization [19], this also applies to CTOs with a similar evidence of myocardial ischemia. Based on the aforementioned chronicity of and adaption to clinical symptoms, the performance of quantitative ischemia tests should be encouraged in asymptomatic patients with CTOs.

Improvement of LV function

In studies on PCI for CTOs from the late 1990s and early 2000s, the number of patients included with a prior MI varied between 36 and 68% [22,23,61–66]. These are the patients who will typically demonstrate regional LV dysfunction, but these are also the patients who will have the highest likelihood of a discernible change of LV function during follow-up [67].

The potential effect of a reopened CTO on LV function was established early on with the first attempts to treat CTOs by PCI, but again no randomized trial was performed, and the only comparisons are derived from comparing failed and successful PCI attempts. When reviewing these early studies, one needs to keep in mind that they were performed with balloon angioplasty alone, or with bare metal stents later on, but not with drug-eluting stents. Lesion recurrence as a major detrimental factor for the functional improvement was very high in these studies [67]. The effect of global LV function as assessed by ejection fraction (EF) is generally less pronounced than the effect on regional function. Melchior *et al.* were among the first to observe a slightly improved left ventricular ejection fraction (LVEF) by 4% 48 months after PCI, and reported an improved regional contractility and relaxation index [68]. Engelstein *et al.* observed a difference in improvement over a period of 10 months only in case of persistent vessel patency with an increase of LVEF by 6.7% and an improved regional function, with no changes over time in case of reoccluded vessels [69]. A similar observation with regard to patent and reoccluded arteries was reported by Danchin *et al.*, who found an increase of LVEF by 7% and improved regional function. They also mention prevention of LV remodeling through the prevention of an increase of LV end-diastolic volume in patients with a prior MI and a patent artery at follow-up [70]. Van Belle *et al.* applied systematic bare metal stenting, thus preventing reocclusion in their small series of 22 patients, and observed an improvement in global and regional LV function, as well as improved remodeling [71]. Sirnes *et al.* assessed LV function over 6 months within a randomized controlled trial comparing balloon angioplasty and bare metal stenting for CTOs. They observed a significant increase of LVEF by 5% and of regional function dependent on the patency of the treated artery in 95 patients [72]. The largest body of data was reported by Dzavik *et al.* from the TOSCA trial also comparing balloon angioplasty with bare metal stent implantation. The improvement of LVEF was significant among the 244 patients available for quantitative analysis but made up only 1.6% in absolute difference. They analyzed possible predictors of improvement and determined a shorter duration of occlusion (<6 months) and a more severely impaired LV function at baseline (<60%) to predict a possible improvement after PCI [73]. Chung *et al.* compared the changes in LV function after successful recanalization in patients with and without a prior MI. They observed an improved LVEF by 7.8% from 59.5% at baseline in patients without a prior MI, and a nonsignificant improvement by 1.6% from 48.9% at baseline in patients with a prior MI [74].

In case of ischemia-related regional impairment as assessed by dobutamine stress echocardiography, the functional recovery may take place immediately after a successful PCI [75]. Regional dysfunction *per se* observed by angiography or echocardiography may not discriminate between irreversibly damaged or hibernating myocardium. Recovery of LV function in

chronically ischemic myocardium depends on the presence of hibernating or stunned but viable myocardium [76,77]. LV recovery starts within 1–4 weeks after revascularization and is usually complete within 3 months [78–80]. Although these studies were performed after surgical revascularization, they are probably also applicable to PCI. Most studies cited above evaluated LV recovery after PCI at a follow-up of 6–12 months. In rare cases, however, LV recovery may take longer then expected as shown by an anecdotal observation of complete resolution of severe ischemic cardiomyopathy due to a proximal left anterior descending coronary artery (LAD) occlusion after 2 years of vessel patency [81].

In order to improve LV function even in patients with regional wall motion abnormality due to a CTO, a study recently infused circulating progenitor cells into a previously recanalized and patent CTO. The infusion was performed within 10 days of the initial recanalization, thus also including the benefit transmitted by the open artery *per se*. An improvement of global and regional LV function was observed by cardiac MRI within 3 months, and even a reduction in infarct size from 14.4 to 11.6%. The further follow-up at 15 months showed slight additional improvements, which were not apparent in the control group without cell infusion [82]. This was a randomized study in a small group of 28 patients, where the improvement of LVEF by 7% from 51% was in a range also observed in some of the aforementioned studies. By contrast, there was no improvement in the group without infusion, which is unexpected given the fact that reopening the artery alone already should lead to functional improvement, as shown in several hundred patients included in the aforementioned studies.

A unanimous finding of all the studies examining LV recovery was the need for persistent patency of the recanalized artery. This was difficult to achieve in the era of balloon angioplasty and bare metal stents, but is now improved in the era of drug-eluting stents.

LV function & viability

Less homogenous observations are made with respect to the influence of a prior MI. The definition of a prior MI in these studies was not comparable and may have relied on clinical records, on the EKG finding of Q waves, or on the subjective recollection of the patient alone. The nature of the previous MI, however, is certainly the key issue, and it may explain some of the differences or even contradictory findings, for example, in the studies of Dzavik and Chung [73,74]. With EKGs as the main criteria of a previous transmural infarction, there may have been uncertainties until the advent of modern imaging modalities such as MRI. However, the EKG is still invaluable for those occlusions were the leads relate to a certain angiographic finding, such as the inferior leads for a right coronary artery occlusion, and the chest leads for a left anterior descending artery occlusion. The absence of Q waves in these two frequent sites of CTOs was a perfect predictor for functional recovery [83]. The 12-lead EKG criteria cannot be applied in all patients due to the presence of bundle branch blocks, but in those 42 out of 63 patients with regional wall motion abnormality it was as valuable as a more expensive MRI would have been [84].

Myocardial viability can be assessed by noninvasive imaging modalities such as dobutamine stress echocardiography, contrast echocardiography and nuclear scintigraphic methods such as single photon emission computed tomography and positron emission tomography. Echocardiography depends on good imaging quality not available for all patients. Nuclear studies using technetium (^{99m}Tc) or thallium (^{201}Tl) have the problem of limited spatial resolution and attenuation artefacts, and they may not perfectly differentiate between ischemia-related hypoperfusion and persistent hypoperfusion due to scar tissue, which is attempted to overcome by additional bolus injections at the end of the stress protocol. The gold standard for viability testing had been positron emission tomography assessment of myocardial perfusion and metabolism using differential tracers of ^{13}N-labeled ammonia and ^{18}F-fluorodeoxyglucose, however, the scanners are not widely available. Therefore, MRI certainly is now the gold standard to detect irreversibly damaged myocardial scar tissue, and helps to indicate surgical and interventional revascularization. The only limitation would be cost issues, and of course the presence of implanted devices, whereas its availability is now almost universal [85]. When MRI is applied to patients with a CTO, the transmural extent of late enhancement and also the residual wall thickness of viable myocardium are related to the improvement of LV function after PCI [84,86]. The transmural extent of late enhancement is a readily available measure, however, a linear relation with LV recovery is difficult to establish as the spatial extent among other factors needs to be considered as well. Presently, cutoff values of certain improvement are given with an extent

less than 25% of wall thickness, with a large grey zone of 25–75% with uncertainty of recovery. Some further improvement can be expected in this grey zone between 6 months and 3 years after PCI, but these improvements are moderate [87]. No recovery is expected with a complete transmural extent of the scar tissue.

MRI with its high spatial resolution and no need for radiation can also help to assess the effect of recanalizing a CTO early and late after the procedure. Increased myocardial blood flow was demonstrated within 24 h of the procedure together with an improvement in contractility [88]. An integrative approach of functional assessment together with assessment of viability are the ideal application and approach of MRI in CTOs [89].

These modern imaging modalities can aid the decision making process, but there remain uncertainties in the large grey zone area of partially late enhancement extent. Around every trasmural infarct there are border zones with less transmural and more endocardial scars, which require the additional evaluation of the residual and reversible ischemic burden in this territory. The clinical decision can be aided by these tools, but other factors need to be taken into account such as the age of the patient, the extent of coronary artery disease, and the patients general life expectancy.

With increasing success rates and a low complication rate of PCI for CTOs, a number of patients with ischemic cardiomyopathy will be selected for revascularization. Those patients meeting the Multi-center Autonomic Defibrillator Implantation Trial (MADIT) criteria for prophylactic implantable cardioverter-defibrillator (ICD) treatment need specific consideration. In order to plan their revascularization strategy they should undergo a baseline MRI study to determine the indication for PCI, and then, irrespective of a subsequently planned PCI or CABG, should receive an ICD before PCI, also because of the need for dual antiplatelet therapy after PCI. There are preliminary data from a Spanish registry of ICD patients in which patients with an untreated CTO had more ICD interventions during follow-up than those who were revascularized [Louis Nombela, Pers. Comm.]. One could argue that the ICD should be implanted after a failed recovery of LV function, but as it cannot be predicted whether LV recovery will lead to an improvement of LVEF that eventually exceeds the cutoff of the MADIT criteria, ICD implantation should be considered and discussed with the patient as the first step.

Improvement of survival

No single large randomized clinical trial on revascularization versus medical therapy in patients with stable angina pectoris could show an improvement of survival. Still the debate is ongoing as to whether the individual trials had enough power to detect a prognostic difference [42]. A recent meta-analysis concluded that there is indication of a survival benefit when treating patients with stable angina by PCI [90], but this opinion is not uniformly supported and needs further corroboration by a larger scale future randomized trial [91].

As previously mentioned, CTOs present the perfect example of a stable coronary lesion. If there would be a greater survival benefit expected from revascularizing a CTO as compared with a nonoccluded lesion is unclear and can be argued on theoretical grounds quite controversially, in the absence of any solid data. A nonoccluded lesion carries the risk of further lesion progression, and becoming the site of an unstable or even infarct-related lesion in addition to the ischemic burden it provides in case of lesion progression in other vessel territories. There is still uncertainty about the general risk of lesion progression especially in the era of optimized medical therapy with aggressive lipid lowering goals [92]. A CTO cannot progress as it is already occluded and stabilized by collaterals. The major impact on prognosis if left untreated results from the progression of coronary artery disease in remote vessel regions, especially collateral donor arteries, and from the risk of recurrent myocardial ischemia that may also trigger arrhythmic events.

The fact that the risk of leaving a CTO alone is not negligible is highlighted by the observation of the severe prognostic impact on outcome if an acute MI occurs in the presence of a CTO in one of the other arteries. The 30-day mortality is tripled despite the treatment for STEMI by primary PCI [14], and the incidence of cardiogenic shock increased [15]. The further long-term prognosis of the initial survivors is adversely influenced through a follow-up of 5 years [93]. This observation is the basis for a randomized trial addressing the specific coincidence of a CTO in patients undergoing primary PCI. In the EXPLORE trial patients will be randomized to receive an additional PCI for the CTO within 7 days of their primary PCI or be treated medically through follow-up [94].

Multivessel disease & CTOs

As compared with nonoccluded lesions, the frequency of a future MI may be lower in CTOs, as one territory is already occluded, however, the

severity of such an event carries a higher mortality risk. In addition, continuing ischemic burden may cause a deterioration of LV function over time and progressive physical limitations. Taken together, there may be an even greater benefit derived from revascularizing a CTO than from PCI in a nonoccluded vessel, as the decision making process, especially in multivessel disease, of which lesion should be treated is often difficult. The recent FAME study underscored the problems in deciding which nonoccluded lesion requires treatment, by comparing a fractional flow reserve-based treatment of coronary lesions in multivessel disease to the angiographic severity-based assessment, which remains the standard approach in clinical practice today. The study showed that the routine assessment by eyeballing carries a high likelihood of overtreatment, and thus unnecessary complications without improving the clinical outcome, as well as a lower but considerable risk of missing significant lesions [57].

Another consequence from the FAME trial might be the need to reconsider the concept of complete revascularization, which is the main goal for surgical revascularization, and which is also extended to PCI treatment [95]. Its effect on the outcome in comparative trials between CABG and PCI remains unclear [96,97]. This could be partly explained by the fact that completeness of revascularization both in trials as well as in daily practice is based on the visual and not the functional assessment. PCI is at a disadvantage in this situation, as the treatment of insignificant lesions induces increased risks during follow-up [98,99], whereas a graft placed on a nonsignificant lesion during surgery will not increase the risk of the procedure, and its higher likelihood of graft closure during follow-up will have little consequence [100].

If we take the aforementioned into consideration when discussing the relevance of a CTO for long-term prognosis in multivessel disease there can be hardly any doubt on the hemodynamic significance of such a lesion. Not revascularizing a CTO results in an incomplete revascularization. The New York State Registry database showed a considerable additional adverse effect on survival if a CTO was one of the lesions that was incompletely revascularized [101]. Likewise, a recent study from Italy demonstrated an additional negative impact on survival in patients with multivessel-disease and untreated CTOs [102]. While in the New York State Registry the difference in mortality was approximately 1% after 3 years, it was 10% in the Italian study, which emphasizes the problems in using registries with different entry criteria and selection bias to quantify clinical risks.

The Italian registry is one of the most recent of a series of registries that tried to assess the impact of a successful recanalization of a CTO on clinical outcome, and specifically survival. There are now several thousand patients included in these registries, which all have the major basic setback, that the patients with successful PCI were compared with those in whom the procedure had failed, thus, there is no pure conservative arm in any of these registries. Still, the large number of patients presented in these trials cannot be ignored as a strong argument that revascularizing a CTO may be of prognostic benefit.

Registries on the impact on survival

Suero *et al.* from the Mid-America Heart Institute (MO, USA) were the first to present data on 2007 patients with a CTO treated during a long period of 20 years in one of the pioneering centers of CTO treatment [18]. The 10-year survival rate was significantly lower for the patients without revascularization (65.1%) than for those with successful revascularization (73.5%). Further subanalysis revealed that the effect of revascularization was less pronounced in diabetic patients [103], and that the CTO of the left anterior descending artery was the singular vessel location that changed survival, and no prognostic effect was observed in patients undergoing revascularization of the right or circumflex artery [104].

Over a shorter time period and with less patients, Hoye *et al.* reported similar observations from the Thoraxcentre in Rotterdam [105]. They followed up 874 CTO patients for an average of 4.1 years and reported a survival rate of 93.5% in patients with successful PCI for a CTO as compared with 88% with an unsuccessful procedure. The major adverse cardiovascular event-free survival rate was significantly higher for the patients with a successful PCI (63.7%) than for those in whom revascularization failed (41.7%). They found that successful revascularization, young age, absence of diabetes and absence of multivessel disease were the main factors leading to a favorable result. More recently, Aziz *et al.* reported that the mortality rate of CTO patients for 2 years after treatment was significantly lower when revascularization was successful (2.5%), than when it was unsuccessful (7.3%) [106]. In the most recent large registry, Muramatsu *et al.* report on 606 patients who underwent PCI for at least one CTO during 1996–2005,

again a historic cohort but extended to the era of drug-eluting stents and modern recanalization techniques [107]. They compared the group of 436 patients with persistent patent arteries at follow-up with those 170 patients with initial or late failure of patency. The overall survival rate was 92% after 6 years with a patent artery, and 64% with an occluded artery. Interestingly, the authors also report an improved survival in those patients in whom by echocardiographic criteria of akinesia no viability was suspected. The mode of death during follow-up was related to an acute MI (43%), mainly due to the incidence of a remote vessel occlusion in more than half of all patients. Congestive heart failure preceded death in one third of patients. This registry stands out from the other data as it takes early failure and late reocclusion together and basically presents the comparison of long-term patent and (re) occluded CTOs. The persistent patency might be an important additional factor for the prognostic benefit, which is clearly better nowadays with drug-eluting stents than it had been in the era of balloon angioplasty and bare metal stents.

There are additional reports on similar registry cohorts not published in full length. A Canadian group of expert operators presented at the American Heart Association Scientific Meeting in 2001 their survival data from 1488 patients over 6 years, also observing an absolute survival benefit of appoximately 10% after successful versus unsuccessful recanalization. Most recently, the combined registry of the Milan and Columbia operators presented similar observations from a more contemporary time period at the TCT Scientific Session in 2009. In 1362 patients, the difference in mortality between successful and unsuccessful PCI was 3.6 versus 8.7% after 3 years of follow-up.

In all the aforementioned registries, the rate of successful recanalization was in the range of 60–75%, well below the level that is achieved by experts using the latest technical approaches and developments [38]. If we look at the medical arm of the COURAGE trial, there were 8.3% deaths reported during follow-up which averaged 4.6 years [42]. If we look at the mortality in the CTO registries in patients with failed procedures, there are considerable differences and it is hard to compare the various mortalities. Some of the larger registries with long-term follow-up are summarized in Table 1 together with the COURAGE study treatment arms. To evaluate and account for differences in follow-up, the

Table 1. Registries of percutaneous coronary intervention for chronic total coronary occlusion assessing long-term outcome between successful and unsuccessful procedures.

Author (years); follow-up	Outcome	n	Age (mean)	Diabetes (%)	Prior MI (%)	LVEF (%)	LAD (%)	RCA (%)	Death overall (%)	Death at 3 years (%)	Ref.
Ivanhoe *et al.* (1980–1988); 4 years	Successful Unsuccessful	317 163	55 56	10 15	56 53	55 56	48 33	29 44	1 4	1 3	[46]
Angioi *et al.* (1983–1991); 3.6 years	Successful Unsuccessful	93 108	55 56	10 11	54 66	59 59	40 38	35 39	3 8	3 8	[47]
Noguchi *et al.* (1986–1996); 4.3 years	Successful Unsuccessful	134 92	61 61	26 32	36 51	56 54	49 44	39 35	5 24	1 3	[115]
Suero *et al.* (1980–1999); 10 years	Successful Unsuccessful	1491 514	60 61	21 20	56 52	51 52	36 36	38 38	26 33	4 15	[18]
Hoye *et al.* (1992–2002); 4.5 years	Successful Unsuccessful	567 304	60 61	12 9	56 49	NA NA	33 27	42 53	7 17	5 9	[105]
Drozd *et al.* (1996–2003); 2.5 years	Successful Unsuccessful	298 161	57 58	11 11	73 66	NA NA	NA NA	NA NA	2 3		[49]
Aziz *et al.* (2000–2004); 1.7 years	Successful Unsuccessful	377 166	59 59	14 9	58 58	53 53	44 34	39 44	2 7		[106]
Prasad *et al.* (1979–2005); 10 years	Successful Unsuccessful	914 348	63 64	NA NA	33 42	NA NA	NA NA	NA NA	25 31	6 6	[108]
Valenti *et al.* (2003–2006); 2 years	Successful Unsuccessful	344 142	67 70	24 21	45 54	42 41	27 33	44 36	5 12		[102]
Muramatsu *et al.* (1996–2003); 5 years	Successful Unsuccessful	436 170	66 69	46 53	54 50	53 53	48 49	40 42	8 36	4 25	[107]
COURAGE (1999–2004)	PCI arm Medical	1149 1138	62 62	32 35	38 39	61 61	NA NA	NA NA	7 8	4 4	[42]

Only registries with at least 200 patients and a follow-up of more than 1 year are presented.
LAD: Left anterior descending coronary artery; MI: Myocardial infarction; NA: Not available; PCI: Percutaneous coronary intervention; RCA: Right coronary artery.

data shown in Table 1 try to compare the different treatment arms at the same theoretical time point of 3 years of follow-up. Additional clinical factors that seem to influence survival such as diabetes and LV function are given to make comparisons between registries more plausible. In COURAGE, the mortality after 3 years was approximately 4% in both arms. In many of the registries the survival of the PCI group was in a similar range or lower than in COURAGE, and only two registries stand out with a considerably worse outcome in the unsuccessful arm (i.e., Suero *et al.* [18], and the recent data from Muramatsu *et al.* [107]). The latter specifically highlights the importance of persistent patency for the prognosis.

Another large registry analysis from the Mayo Clinic with a differing observation with no adverse effect of a failed procedure on survival should be mentioned [108]. The problem with this registry is the very long time period that it spans, and the fact that PCI for a CTO was not a frequent indication in the overall PCI volume of this center. For further detailed analysis of additional smaller registries one may refer to a recent meta-analysis concluding that there seems to be evidence for a survival benefit, but with the caveat of lack of randomized data, and above all lack of a true comparison with a conservative treatment arm [43].

Surgery or PCI for revascularization of a CTO (insights from the SYNTAX trial)

Despite the absence of randomized studies to answer the question as to whether a CTO should be revascularized or be treated conservatively in general, the guidelines on revascularization clearly state that a CTO like any other coronary lesion requires revascularization if it causes symptoms or ischemia of more than 10% of the myocardial territory [19]. Which course of revascularization to take, surgery or PCI, is not clearly defined and should also depend on factors such as the presence of multivessel disease, involvement of the left main coronary artery, impairment of LV function as well as the general prognosis and comorbidity of a patient. The success rate of a proposed PCI for a CTO must also be taken into consideration as compared with alternative modes. Recently, a review of surgical outcomes reported on the extremely high efficiency of a minimally invasive direct coronary artery bypass (MIDCAB) procedure for CTOs of the left anterior descending artery [109]. However, one needs to also take into account that the surgical mortality as low as it may be is still a greater risk than with PCI, and even if a low number of deaths does not statistically influence outcomes summarized as a composite of major adverse cardiovascular events, this still is not negligible. This should be considered when assessing, for example, a randomized trial of stenting versus MIDCAB for singular left anterior descending artery lesions, in which two of 100 patients died in the MIDCAB arm [110].

A direct comparison of PCI versus CABG for CTO revascularization is only available within the context of larger randomized trials [96,97], but the number of included CTOs is very low and the presence of CTOs was typically a frequent reason for not randomizing a patient because of the low expected success rate of PCI [111]. A subanalysis of patients with CTOs from these trials would be very limited in its broad applicability. Finally, however, the SYNTAX trial included a considerable number of patients with a CTO that made a meaningful subanalysis possible, despite the fact that like in the classic BARI trial in this contemporary trial the presence of a CTO was a major reason not to randomize patients and refer them to the parallel CABG registry [112].

The subanalysis of patients with a CTO randomized in the SYNTAX trial has not been published as yet, but has been presented at several scientific meetings. The subanalysis of CTOs as presented at the CRT meeting in Washington 2009 by Serruys revealed that more than one fourth of all patients randomized in SYNTAX had at least one CTO. The per lesion representation of CTOs was approximately 7.5%. The comparison of 244 patients with a CTO randomized to PCI and 235 with a CTO randomized to CABG provides a relatively large patient group to derive meaningful information. Overall, the outcome in the subgroup with CTOs was similar to the general outcome in SYNTAX, meaning that hard end points of mortality and MI were comparable, with a higher need for repeat revascularization after PCI [113]. One would have expected a difference due to a higher rate of surgical revascularization of CTOs, but the analysis of the CTO segments showed a rather low success rate also in the surgical group. Only 68% of occluded segments were revascularized by placing a graft, as compared with 49% in the PCI group of successful opening of the occluded segment. It should be noted that not all CTOs were attempted in both groups. Not surprisingly, the completeness of revascularization as a major quality criteria for surgery was just 49.6% in the 236 patients with a CTO.

For the PCI group in SYNTAX it needs to be stated that the approach in these patients with multivessel disease was rather aggressive regarding the goal to perform multiple interventions during one session. Only 20% of procedures in patients with a CTO were staged, an approach which is currently not advised for the treatment of complex CTOs [3]. The low success rate of 53% in 250 attempted CTOs is also not a mark that is typical for the contemporary approach to CTOs, and the current guidelines even state that a CTO should only be approached if the operator's experience will make a success rate above 80% achievable.

In summary, the SYNTAX trial needs to be commended in that it was the first trial not to shy away from the complexity of CTOs in this randomized comparison with CABG. But the standard approach to CTOs, which would require staged sessions performed by dedicated operators, was not up to the level of success that is achievable even outside of Japan with its dedicated CTO experts. Still, the comparison with CABG showed no inferiority regarding hard end points, and provides room for speculation that with the latest generation drug-eluting stents and a higher success rate, the comparison with surgery might have been even more favorable.

The SYNTAX trial introduced the SYNTAX score, which receives much attention now as a selection tool for deciding the appropriate revascularization strategy [113]. Within this score, extreme weight is given to the presence of a CTO [114]. In the face of further subanalysis from the trial and even introduction of the score in the recent guidelines [19], the impact of observing a CTO in the context of multivessel disease would be to shift the decision towards surgery, despite the aforementioned excellent outcome of the PCI arm in the CTO subgroup. The weight given to CTOs in the SYNTAX score is arbitrary, and requires careful re-evaluation in the face of the improved technical approach and outcome, which was not practiced in the SYNTAX trial.

A typical case example

Figure 1 depicts the angiogram of a patient with a CTO of the right coronary artery (RCA), which was well collateralized by a presumably preformed large transapical collateral from the LAD. The patient was asymptomatic until the incidence of an acute coronary syndrome caused by a plaque rupture and subtotal occlusion of the mid LAD (shown by the arrow in Figure 1A & 1B). In the initial angiogram, the distal RCA is filled via collaterals from the circumflex artery (arrowheads, Figure 1A). Only after treating the LAD lesion with a stent (between arrows, Figure 1C) the main collateral supply via the apex is taking over again the filling of the posterior descending branch of the RCA (arrowheads, Figure 1C). If no additional collateral channels existed, this would be a patient suffering from a large ischemic territory; due to the collateral supply the LV function was fully preserved (Figure 1D). After the acute intervention, the patient underwent a stress test and assessment of oxygen uptake, before the RCA was recanalized. The lesion which consists of a shorter proximal and a longer medial occluded segment can be evaluated from the double injection filling in Figure 1E. After recanalization and implantation of five everolimus-eluting stents (between arrows, Figure 1F) the perfusion was excellent. A follow-up angiography was performed 7 months later with an excellent long-term result (Figure 1G). At follow-up, the repeated oxygen uptake measurement showed an increase of maximum oxygen uptake from 22.7 ml/kg/min to 29.6 at follow-up, with an additional increase in maximum exercise level from 131 to 156 Watts.

This typical case highlights the unrecognized and longstanding RCA occlusion that did not cause typical angina pectoris, but an objective lower exercise capacity than that achievable after recanalization. Most importantly, it is the typical situation where a CTO becomes evident during an acute event in a collateral donor artery. In this particular patient, the presence of coexisting collateral pathways could compensate for the loss of the major collateral supply. In the absence of such coexisting collaterals the patient might have been hemodynamically compromised [14,15].

Future perspective

There is convincing evidence to support the decision to revascularize a CTO in case of symptoms (angina and dyspnea) and viability, and it is in accord with the recommendations of recent guidelines for myocardial revascularization [19]. Despite this, the number of CTO treated by PCI is clearly under-representing the actual prevalence of these lesions, which has not changed over the past decade [9,13]. The advent of drug-eluting stents enables a patency rate of recanalized CTOs similar to that of nonocclusive lesions. Advancements over the past decade improved the interventional success rate to a range that is close to what is generally reported for nonocclusive lesions [37,38].

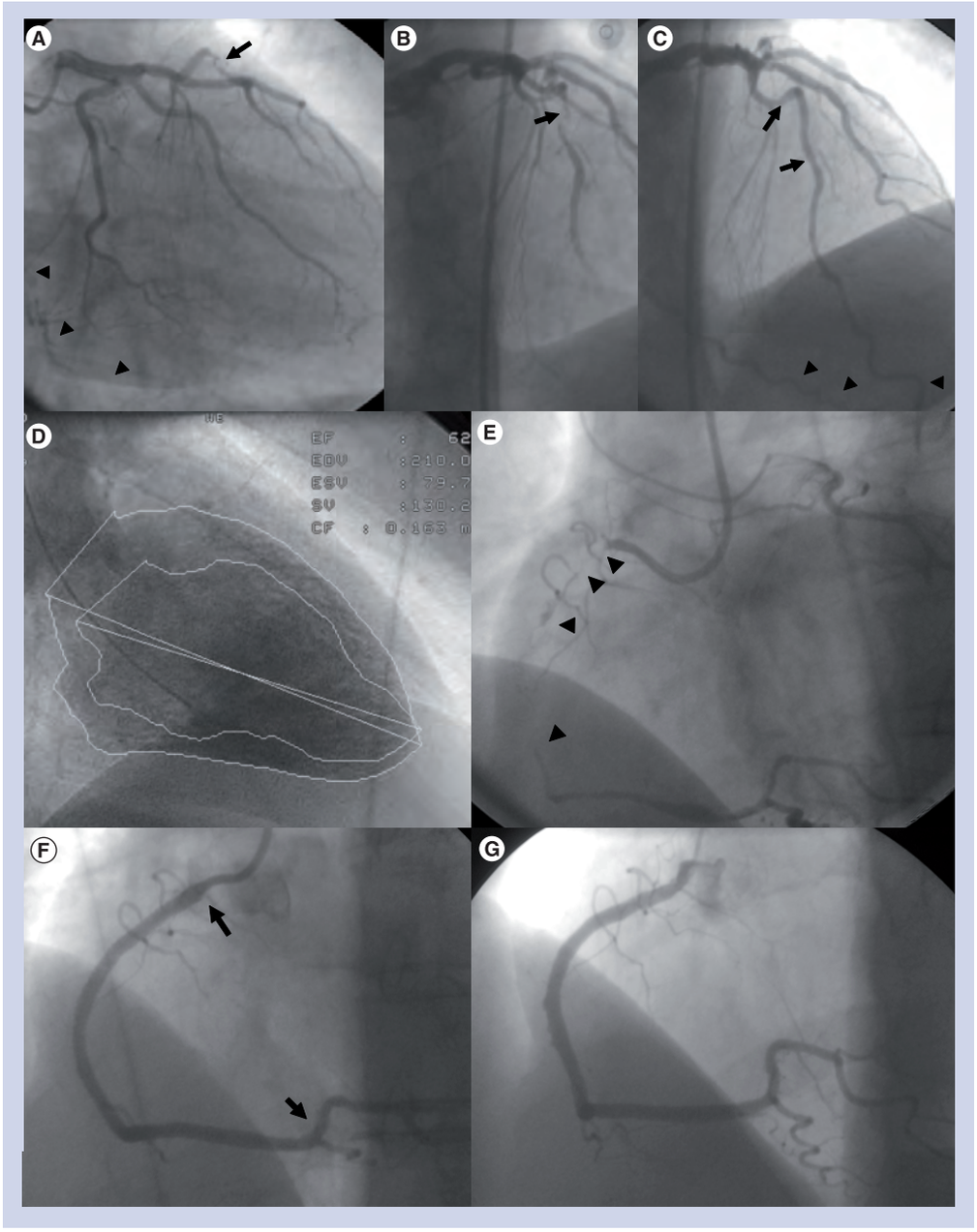

Figure 1. Asymptomatic chronic total coronary occlusion of the right coronary artery, discovered during an episode of acute coronary syndrome related to the left anterior descending artery.

The main reason for the disparity between what is achievable and what is done in general clinical practice for CTOs still appears so great, is the often quoted lack of a randomized trial. The fact that a randomized trial was not conducted before the above advancements in primary and long-term patency had been achieved, can be considered a lucky circumstance, as such a trial might have failed due to the technical deficiencies at that time. However, it is now time with all the advances at hand, to enter into such an endeavor and answer the question of a benefit in clinical and prognostic outcome of revascularizing a CTO by PCI. The main question to be addressed is whether a clinical benefit is provided by PCI without an increased risk, an issue that was raised in the COURAGE trial [42]. Whether a prognostic benefit can be observed depends mainly on the underlying risk of the patient population, as highlighted by the differences observed in the previous registries (Table 1). In fact, two trials are in the process of being launched or are ongoing which will address this question, one conducted under the

lead of the European Chronic Total Occlusions Club [201], the EURO-CTO trial, and another trial that has been registered with clinicaltrials.gov, DECISION-CTO [202] to be conducted in South Korea. The results of these trials will not be available for another 5 years, and may not solve all the associated issues, but they show that this important issue will remain in the focus of interest during the near future.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

Chronic total coronary occlusions are a unique type of coronary lesions

- Chronic total coronary occlusion (CTO) is defined as a lesion without any antegrade flow (Thrombolysis In Myocardial Infarction 0) that has persisted for at least 3 months.

Prevalence

- CTOs are found in 20–30% of patients with angiographic diagnosis of coronary artery disease.
- They only constitute 6–10% of target lesions for percutaneous coronary intervention (PCI).
- Indication for treatment should be based on relief of symptoms, improvement of left ventricular function, and/or improved survival.

Time to reconsider PCI for CTOs

- The long-term patency of CTOs is significantly reduced with drug-eluting stents and similar to nonocclusive lesions.
- The technical success rate is considerably improved by advanced recanalization techniques to almost 90%.

Relief of symptoms after PCI for CTOs

- Reduced level of angina pectoris and improved quality of life with successful PCI has been reported.

Improvement of left ventricular function after PCI for CTOs

- Global and regional left ventricular function improve in case of a successful recanalization of a CTO and maintained patency.
- The presence of myocardial viability is crucial for the functional improvement after recanalization of a CTO.
- MRI provides the gold standard for the assessment of viability before PCI for CTOs.

Improvement of survival after PCI for CTOs

- There is a threefold increase in mortality in patients who suffer a STEMI if a CTO is present.
- A complete complete revascularization that includes the revascularization of a CTO improves survival.
- The successful PCI of a CTO improves survival as compared to a failed PCI for CTOs.

Surgery or PCI for revascularization of a CTO

- The SYNTAX study shows no advantage of surgery over PCI with respect to death and MI.
- The SYNTAX study shows an increased need for repeat revascularization.
- The levels of revascularization in the SYNTAX trial for CTOs do not represent contemporary success rates.

Future perspective

- Application of current guidelines and evidence should lead to an increase in PCI volume for CTOs.
- Randomized trials are required to establish the benefit of modern PCI techniques on clinical outcome in CTOs.

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