CORONARY CHRONIC TOTAL OCCLUSIONS IN THE SETTING OF ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Approximately 10-15% of ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) are found to have a chronic total occlusion (CTO) in a non-infarct related artery (IRA). The presence of a coronary CTO in a non-IRA in STEMI patients is associated with increased mortality and above average deterioration of left ventricular function. A number of mechanisms may be responsible for this worsened prognosis, including impaired healing at the infarct border zone, decreased protection against future cardiovascular events, and potentially increased risk of arrhythmias. This review article aims to provide an overview of published data on the prognostic effect of CTOs in a non-IRA in the setting of primary PCI for acute STEMI. Additionally, observational data on staged PCI of CTOs after primary PCI, and future studies on additional CTO PCI after primary PCI, will be reviewed.

Keywords: Chronic total occlusions, percutaneous coronary intervention, acute myocardial infarction, coronary artery disease.

INTRODUCTION

Coronary chronic total occlusions (CTOs) are frequently encountered during coronary angiography. Recent data suggest a prevalence of approximately 10-15% among patients undergoing diagnostic coronary angiography.[1-3] CTOs are regarded as very complex lesions with relatively low procedural success rates, and, even after successful percutaneous coronary intervention (PCI), restenosis rates are 1.5 to 4-times higher compared with non-occluded coronary artery lesions.[4-6] However, the development of drug-eluting stents (DES), specialised equipment such as CTO guidewires and microcatheters, and advanced techniques such as the retrograde approach have made PCI of CTOs a safe and feasible treatment option. At this time, no randomised controlled trials have been completed that compared PCI of CTOs with optimal medical therapy. However, a meta-analysis of a large number of registries comparing outcomes after successful versus failed PCI of CTOs has reported a significant reduction in residual or recurrent angina, a reduced need for coronary artery bypass graft (CABG) surgery, and reduced mortality after successful CTO PCI.[7]

Recent studies in several independent patient cohorts have shown that a concurrent CTO in a non-infarct related artery (IRA) in patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) is associated with a worsened prognosis.[8-12] This review focuses on currently available clinical data concerning concurrent CTOs in non-IRAs in the setting of acute STEMI.

CORONARY CTOS

Definitions and Epidemiology of Coronary CTOs

A coronary CTO is typically defined as a lesion with a 'Thrombolysis in Myocardial Infarction' (TIMI)

score 0 flow, with an estimated duration of at least 3 months.[13] Another term that is frequently used is a total coronary occlusion (TCO), which is frequently defined as a lesion with TIMI 0 or 1 flow and an estimated duration of <3 months. In current literature, these terms are sometimes used interchangeably. This is unfortunate, as there are important distinctions between CTOs and TCOs, e.g. success rates for PCI of CTOs are lower compared with TCOs, and long-term vessel patency after successful PCI is shorter in CTOs compared with TCOs.

CTOs are relatively common; they are found in approximately 10-15% of cases in studies investigating consecutive patients undergoing diagnostic coronary angiography.[1-3] However, percutaneous revascularisation of CTOs is only considered in a small percentage of cases. In the USA, only 5% of all PCIs were performed in CTO lesions, and this attempt rate did not increase between 2004 and 2007.[3] In recent years, this proportion may have increased as a result of operators specialising in CTOs and the development of novel techniques such as the retrograde approach. Data from a Canadian registry of consecutive patients undergoing non-urgent coronary angiography, with no history of prior CABG surgery, between April 2008 and July 2009 (N=9,377) revealed a prevalence of CTOs in 14.7% of patients.[1] The prevalence in patients with coronary artery disease (CAD), defined as at least one lesion >50% stenosis, was 18.4%. Interestingly, only 40% of patients with a CTO had a history of a prior myocardial infarction (MI).

A recent study in 170 consecutive patients with an angiographically documented CTO undergoing late gadolinium enhancement cardiac magnetic resonance imaging (cMRI) also reported that only 42% of patients had previous ischaemic symptoms consistent with MI.[14] However, contrast enhanced cMRI showed that 86% of patients had evidence of a prior MI. Moreover, a small proportion of CTOs might develop not only as a result of a prior acute thrombotic coronary occlusion, but also as a result of progressive coronary stenosis, ultimately resulting in a silent and frequently asymptomatic occlusion.

Are Coronary CTOs Amenable for Percutaneous Coronary Revascularisation?

Coronary CTOs have been named the 'final frontier' in interventional cardiology.[13] Success rates of CTO PCI are lower than success rates of non-occluded lesions, with reported success rates for CTO ranging from about 70-90%.[3,15,16,17] Moreover, CTOs are associated with relatively high rates of restenosis and re-occlusion.[18] However, the advent of DES has reduced target vessel revascularisation rates to about half the rates observed during the bare metal stent era.[5,19]

Novel equipment such as microcatheters, specialised guidewires, and specialised devices such as the Crossboss™ CTO Crossing Catheter and Stingray® CTO Re-Entry System device (Boston Scientific, Natick, MA, USA) have become available in recent years. Furthermore, specialised CTO techniques were developed, such as several techniques for a retrograde approach to interrogate CTO lesions.[20] These developments have led to increased attention for and understanding of CTO PCI, which has led to increased CTO PCI success rates.[16] Despite the complexity of CTO PCI, recent data on the incidence of procedural complications have been reassuring.[17,21]

Coronary CTOs and MI

Coronary CTOs in the setting of STEMI were investigated for the first time in a prospective cohort of consecutive STEMI patients undergoing primary PCI at the Academic Medical Center (AMC) in the University of Amsterdam, Amsterdam, the Netherlands.[8] In this cohort of 1,463 patients, 839 (59%) had single vessel disease (SVD), 30% had multivessel disease (MVD) without a CTO in a non-IRA, and 11% had MVD with a CTO in a non-IRA. This study showed that patients with MVD without a CTO had a 1-year mortality rate comparable to patients with SVD. Whereas, MVD with a CTO in a non-IRA was associated with increased mortality (hazard ratio [HR] 3.8, 95% CI: 2.4-5.9, p<0.001). This study showed that patients with a CTO in a non-IRA undergoing primary PCI for STEMI, had a 1-year mortality rate of 35%. After these initial observations, several researchers have investigated the prognostic impact of a concurrent CTO in a non-IRA in patients undergoing primary PCI for STEMI. Table 1 shows an overview of studies that investigated mortality in STEMI patients with a concurrent CTO in a non-IRA.

A number of mechanisms may explain the markedly increased mortality rate in STEMI patients with a CTO in a non-IRA (Table 2). First, the presence of a CTO in a non-IRA may result in more pronounced negative left ventricular

Table 1: Mortality in STEMI patients undergoing primary PCI with SVD, MVD without CTO, and MVD with a CTO in a non-IRA.

Study	Year	N of patients	Prevalence of CTOs in non-IRA	Follow-up duration	Mortality in SVD, MVD without CTO, and MVD with CTO		
Van der Schaaf et al.[8]	2006	1,417	11.0%	1 year	8%	16%	35%
Claessen et al.[9]	2009	3,277	13.0%	5 years	14%	20%	38%
TAPAS (Lexis et al.)[11]	2011	1,071	8.4%	25 months	8.5%*		15.6%
HORIZONS-AMI (Claessen et al.)[10]	2012	3,283	8.6%	3 years	4.5%	6.7%	34.3%
Bataille et al.[12]	2012	2,020	8.0%	3 years	5.8%	12.1%	34.1%

STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SVD: single vessel disease; MVD: multivessel disease; CTO: chronic total occlusion; IRA: infarct-related artery.
* SVD and MVD without CTO were combined in this study.

Table 2: Potential mechanisms for increased mortality in STEMI patients with a CTO in a non-IRA.

1 More pronounced negative left ventricular remodelling
2 Higher prevalence of suboptimal markers of reperfusion after primary PCI (e.g. absent myocardial blush grade, incomplete ST-segment resolution)
3 Larger infarct size
4 Increased risk of potentially life-threatening arrhythmias
5 Increased prevalence of cardiogenic shock at hospital admission

STEMI: ST-elevation myocardial infarction; CTO: chronic total occlusion; IRA: infarct-related artery; PCI: percutaneous coronary intervention.

remodelling during the first year after the index STEMI. A CTO in a non-IRA was associated with a further decrease in left ventricular ejection fraction (LVEF) in a cohort of 356 patients with serial measurements of LVEF.[9] A baseline measurement was obtained within 1 month after primary PCI, and a follow-up measurement taken within 1 year after the index event. After multivariate analysis, the presence of a CTO in a non-IRA was an independent predictor for further deterioration of LVEF (OR 3.5, 95% CI: 1.6-7.8, p<0.01). In contrast, MVD without a CTO was not associated with a decrease in LVEF.

Second, two studies showed that STEMI patients with a CTO in a non-IRA had impaired markers of reperfusion after primary PCI when compared to patients with MVD without a CTO and to patients with SVD.[10,11] A substudy from the Thrombus Aspiration during primary PCI in Acute ST-elevation myocardial infarction Study (TAPAS) trial showed higher rates of incomplete ST-segment resolution (63.6% versus 48.2%, p=0.005) and higher rates of myocardial blush Grade 0 or 1 (34.2% versus 20.6%, p=0.006) in patients with (versus without) a concurrent CTO.[11] In a substudy from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, patients with a CTO in a non-IRA were found to be more likely to have a post-procedural TIMI flow Grade <3, absent myocardial blush, and incomplete ST-segment resolution.[10]

A third mechanism may be that STEMI patients with a CTO in a non-IRA develop larger infarcts. The aforementioned substudy from TAPAS showed that patients with a CTO in a non-IRA

had higher median levels of maximal myocardial-band of creatinin kinase (CK-MB). A fourth mechanism may be that the presence of a CTO in a non-IRA may lead to an increased susceptibility for life-threatening arrhythmias.[22]

Finally, the presence of a CTO in a non-IRA in STEMI patients is associated with higher rates of cardiogenic shock at hospital admission. In an observational study by Conde-Vela et al.[23] in a cohort of 630 STEMI patients treated with primary PCI, the presence of a CTO in a non-IRA was associated with an increased prevalence of cardiogenic shock at hospital admission, with an OR of 4.48 (95% CI: 2.1-9.1, p<0.001). Hoebers et al.[24] also described a higher prevalence of CTO in patients with (versus without) cardiogenic shock (29% versus 11%).

Coronary CTOs and MI in Selected Subgroups

Cardiogenic shock

The impact of a CTO in a non-IRA in STEMI patients has been studied in several patient subgroups. Two studies investigated STEMI patients presenting with cardiogenic shock,[25,26] defined according to clinical criteria used in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial:[27] hypotension (systolic blood pressure <90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure ≥90 mmHg), and end-organ hypoperfusion (cold extremities or a urine output of <30 ml/hour and a heart rate of ≥60 beats/minute). Both studies showed that the presence of a CTO in a non-IRA was strongly associated with the occurrence of cardiogenic shock at admission. Moreover, a CTO in a non-IRA was independently associated with increased mortality in this extremely high-risk subgroup.[25,26]

Diabetes mellitus (DM)

STEMI patients with diabetes are known to have more extensive CAD. Approximately 35% of STEMI patients without diabetes have MVD compared with 60-70% of diabetic patients.[28-31] In a cohort of 539 STEMI patients with DM undergoing primary PCI, the prevalence of CTOs was also increased; 21% of diabetic patients had a CTO in a non-IRA compared with only 12% of patients without DM (p<0.01).[31] In diabetic STEMI patients undergoing primary PCI, the presence of a CTO in a non-IRA was an independent predictor of 5-year mortality (HR 2.2, 95% CI: 1.3-3.5, p<0.01).

Chronic kidney disease (CKD)

STEMI patients with CKD (defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2) were recently shown to have an increased prevalence of a CTO in a non-IRA (13% in patients with CKD versus 7% in patients without CKD, p=0.0003) in a Canadian cohort of patients (n=1,873) undergoing primary PCI.[32] In patients with CKD, the presence of a CTO was not an independent predictor of mortality. In contrast, a CTO in a non-IRA was an independent predictor of mortality in patients without CKD. Therefore, the clinical impact of a CTO in a non-IRA may be overshadowed by the presence of CKD.

Should We Treat Concurrent CTOs in Acute MI?

The strong association between the presence of a concurrent CTO in a non-IRA in STEMI patients raises the obvious question of whether revascularisation of these CTOs after primary PCI may lead to improved outcomes. Theoretically, this may promote healing at the infarct border zones, improve regional myocardial function, result in less pronounced left ventricular remodelling, and potentially improve electrical stability. In patients with stable CAD, successful CTO PCI has been demonstrated to improve LVEF and reduce left ventricular dimensions.[33-35]

A retrospective study by Yang et al.[36] described 136 STEMI patients with a CTO in a non-IRA who underwent primary PCI, all of whom underwent a staged procedure at 7-10 days after the index procedure to attempt a PCI of the concurrent CTO. This was successful in 64% of patients. During 2-year follow-up, cardiac mortality was lower (8.0% versus 20.4%, p=0.036) in patients with a successful (compared with an unsuccessful) CTO PCI. Moreover, the rate of major adverse cardiac events (MACE: composed of death, recurrent MI, repeat revascularisation, and re-hospitalisation because of heart failure) at 2 years was significantly lower in patients with successful CTO PCI (38.8% versus 21.8%, p=0.042). After multivariable analysis, successful CTO PCI remained associated with reduced mortality and reduced MACE rates at 2 years.

The ongoing Evaluating Xience V and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions after ST-elevation Myocardial Infarction (EXPLORE) trial[37] is enrolling STEMI patients with a CTO in a non-

IRA after successful primary PCI. 300 patients are randomised to either elective PCI of the CTO in a staged procedure within 7 days or to optimal medical therapy. The primary endpoints of this trial are: LVEF and left ventricular end-diastolic volume measured by cardiac MRI at 4-month follow-up. This trial has currently enrolled 80% of patients and will deliver important data regarding the potential beneficial effect of percutaneous recanalisation of concurrent CTOs in STEMI patients.

CONCLUSIONS

Approximately 10-15% of STEMI patients undergoing primary PCI are found to have a CTO in a non-IRA. The presence of a coronary CTO in a non-IRA in STEMI patients is associated with increased mortality, and above average deterioration of left ventricular function. A number of mechanisms may be responsible for this worsened prognosis, including impaired healing at the infarct border zone, decreased protection against future cardiovascular events, and potentially increased risk of arrhythmias. Currently, no prospective studies investigating additional revascularisation of the concurrent CTO have been completed. However, retrospective data suggest a potential benefit of CTO revascularisation in a staged procedure after the primary PCI.[36] The currently ongoing EXPLORE trial will deliver prospective evidence about the potential benefit of staged CTO PCI for this particular patient population.

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