The impact of a chronic total coronary occlusion on clinical outcome

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Publication date
2016
Document Version
Final published version

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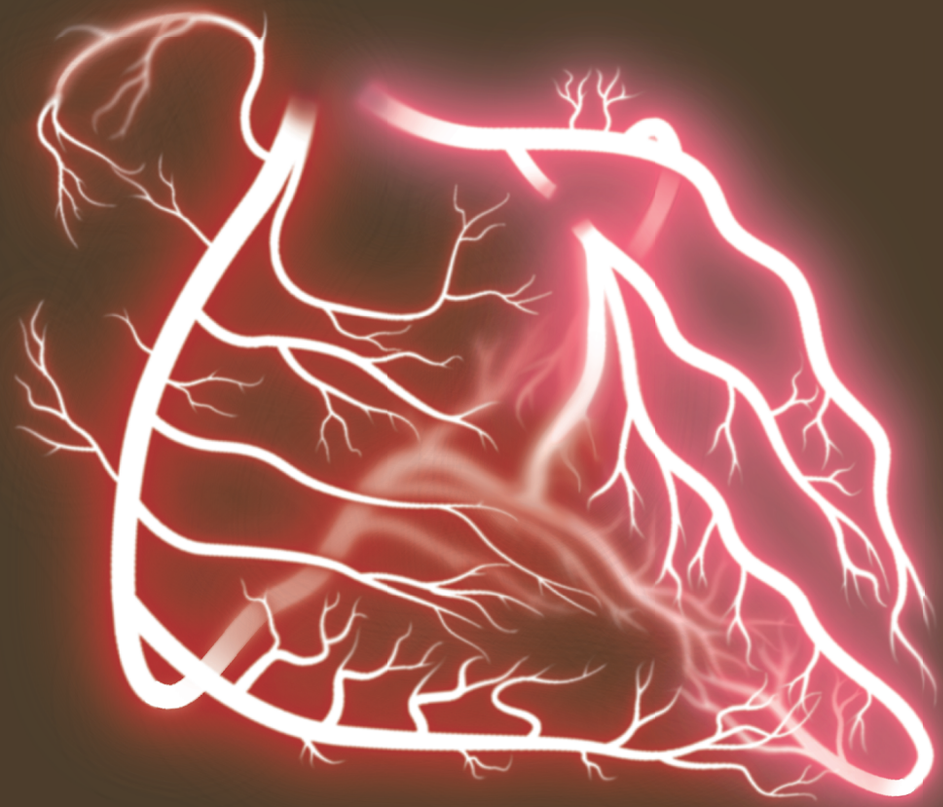

Loes P. C. Hoebers

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The Impact of a Chronic Total Coronary Occlusion on Clinical Outcome.
Dissertation, University of Amsterdam, Amsterdam, The Netherlands

ISBN: 978-94-6169-822-3
Author: Loes Petrus Catharina Hoebers
Cover: Ties van Brussel, tiesworks.com
Lay-out: Optima Grafische Communicatie BV
Printed by: Optima Grafische Communicatie BV

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Additional financial support for publication of this thesis was provided by:
Abbott Vascular, Academic Medical Center – University of Amsterdam, Boehringer Ingelheim, Guerbet Nederland, Pie Medical Imaging, Pfizer, Servier Nederland, Stentys, St. Jude Medical and West Fries Gasthuis Hoorn.

The Impact of a Chronic Total Coronary Occlusion on Clinical Outcome

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 10 november 2016, te 12:00 uur
door
Loes Petrus Catharina Hoebers
geboren te Venray

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Education is an admirable thing, but it is well to remember from time to time that nothing that is worth knowing can be taught.

Oscar Wilde

CONTENTS

Chapter 1

Introduction and outline of the thesis

INTRODUCTION AND OUTLINE OF THE THESIS

The knowledge of the coronary angiogram plays a major role during clinical decision making regarding optimal medical, percutaneous or surgical treatment for coronary artery disease. Therefore, there is a need for detailed information correlating the angiographic anatomic abnormalities with prognostic significance, before treatment effect can be evaluated. Ever since it was possible to view the status of the coronary arteries by angiography in 1958, it is known that mortality increases with the severity and extent of coronary artery disease.[1-4] Multivessel disease is present in more than half of the patients with coronary artery disease and a chronic total occlusion (CTO) is present in approximately 16%. [5,6] Several studies showed an early survival benefit of coronary artery bypass (CABG) surgery versus medical treatment alone in only high risk patients meaning severe coronary artery disease and impaired left ventricular function.[7-10] This observation was absent in studies comparing PCI versus medical treatment only, possibly due to inclusion of low risk patients.[11,12] Thusfar, PCI is mainly performed for symptom relieve only rather than improvement of prognosis, except for patients with an acute myocardial infarction.[11,12] In contrast to stable coronary artery disease, immediate PCI, called primary PCI, in the setting of an acutely occluded vessel is proven to increase survival and reduce recurrent ischemic events.[13] However, mortality rates after primary PCI is still high in several high risk subgroups. These subgroups consist of patients with cardiogenic shock[14], diabetes mellitus[,16] and multivessel disease (MVD). Of the STEMI patients, half are diagnosed with multivessel disease.[17] In 2006, our research group discovered that the increased mortality rate observed in patients with STEMI and multivessel disease, was merely due to the presence of a chronic total occlusion (CTO) in a non-infarct related artery (IRA).[18] After stratification of the MVD-patients into patients with and without a CTO in a non-IRA, patients with MVD without a CTO had a comparable mortality rate to patients with single vessel disease (SVD) whereas the mortality rate of STEMI patients with a CTO was three-fold higher compared to patients with SVD and MVD without a CTO.

The thesis presented here elaborates on this initial finding by exploring which CTO patients carry the highest risk for adverse prognosis and more importantly, to investigate the optimal treatment strategy ranging from medical therapy only to percutaneous coronary intervention and its effect on clinical outcome. There is a lot of controversy whether or not CTOs need to be treated and if so, what criteria should be met such as myocardial viability.[19] Many CTOs receive collateral circulation which provide flow to the myocardium but, this is frequently insufficient to prevent ischemia upon exercise. Several treatment options exist or are under investigation besides medical therapy only, such as the stimulation of arteriogenesis of well-developed coronary anastomoses to improve collateral circulation and thus coronary flow, or CTO revascularization.[20-26] To

date, coronary intervention in stable nonCTO coronary artery disease does not improve prognosis, only symptoms but perhaps CTO revascularization will.[11,12,23]

In **chapter 2**,[27] we describe the current available literature regarding CTO definition, histology, patient characteristics, evidence of treatment, advice for clinical decision making and future perspectives. In **chapter 3**[6], our aim was to get a better understanding of the characteristics of CTO patients and procedures. The best way to accomplish this was to investigate this objective in a large and unselected population. We had the opportunity to work together with Sweden to use the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). The SCAAR registry was established in 1999 after the unification of Swedish Coronary Angiography registry (Acta Coronaria) and the Swedish Coronary Angioplasty registry (SCAP). SCAAR holds data on all consecutive patients from all centers that perform coronary angiography and PCI in Sweden. In this national database with complete consecutive enrolment, we described the prevalence, characteristics and trends of reporting on chronic total occlusions. In **chapter 4**[28] we used the SCAAR database to evaluate the impact of a CTO on prognosis in all patients and in several important subgroups, namely different age categories, diabetes mellitus, gender, severity of coronary artery disease and different procedural indications including STEMI to validate our initial findings which were to determine if the increased mortality seen in STEMI patient was indeed due to the presence of a CTO. This finding was also confirmed in other cohorts;[29-31] however, the majority of the studies were hampered by the single center nature and small cohort sizes, all not applicable in SCAAR.

In patients with stable coronary artery disease, the elderly represents a large proportion of the daily clinical ''real world'' practice, the need for more information is high as the anticipated benefits and possible risks of many treatments can differ with age. However, the absence of clinical data in the elderly population should not imply a non-performance of PCI due to perception of prohibitive complications or low success rate in this population. Therefore, the aim of the study in **chapter 5**[32] was to investigate the procedural success rates and long-term clinical outcome of successful versus failed CTO revascularization in patients ≥75 years. PCI of CTOs may have a beneficial effect on survival through a better preserved or improved LVEF. Therefore, in **chapter 6**[33] we performed a meta-analysis on all available literature describing the impact of successful CTO PCI on left ventricular function and additionally evaluated the literature reporting long-term mortality after successful versus failed CTO PCI. As our meta-analysis showed, in the elective setting successful versus failed PCI was associated with improved clinical outcome.

In part III we describe the impact of a CTO in patients with an acute myocardial infarction. We investigated the impact of MVD with and without a CTO in several high risk subgroups in the AMC-cohort, namely STEMI patients with diabetes mellitus, **chapter 7**,[34] and STEMI patients stratified for the presence of cardiogenic shock upon presenta-

tion to the cathlab, **chapter 8**.[35] In STEMI patients the mortality is most severe when the culprit vessel is the left descending coronary artery as it supplies the most important part of the left ventricle. In STEMI patients with MVD and a CTO, there is always one acutely occluded vessel and one chronically occluded vessel. For this reason, we evaluated the prognosis of STEMI patients based on the location of the CTO and culprit lesion in **chapter 9**.[36]

The question still remains if a CTO is just a marker of adverse prognosis or that a causative relation exists. If so, revascularization may counteract the adverse prognosis observed in patients with MVD and a CTO. Thusfar, additional PCI of other significant nonCTO lesions in the acute setting does not seem to majorly affect prognosis, **chapter 10** and **11**.[37,38] Large randomized controlled trials are needed to evaluate the possible beneficial effect of CTO revascularisation in STEMI patients without CS and complete revascularisation in STEMI patients with CS. Therefore we initiated a global multicenter randomized controlled trial in non-CS STEMI patients, to investigate a possible beneficial effect of opening a CTO in a non-IRA in a staged PCI procedure within one week after STEMI on left ventricular ejection fraction (LVEF) and left ventricular dimensions: the EXPLORE (Evaluating XIENCE V and LVF in PCI on Occlusions after STEMI) trial, **chapter 12**.[39] CTO revascularization during the primary procedure is not feasible as its success depends largely on the operator's experience, lengthens the procedure considerably with also increased use of contrast media and fluoroscopy time. Therefore, we scheduled the procedure in the semi-acute phase. There are two main mechanisms involved in the hypothesis of the Explore trial. First, recanalization of the CTO will possibly restore the contractile function of the hibernating myocardium. Furthermore, recanalization of the CTO might improve the healing of the infarct border zone. This assumption is based on the coronary anatomy where the perfusion area of the infarct related coronary artery and the CTO are adjacent or overlapping. In recently perfused myocardium, the revascularization of a CTO will improve the myocardial perfusion in this overlapping region and therefore might improve the healing of this border zone and might protect against negative remodelling with preservation of left ventricular function. The latter mechanism is also one of the reasons why we believe that this procedure is best performed in the first week after STEMI. The results of the EXPLORE trial, is presented in **chapter 13.**[40]

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Part I

Patients with a chronic total coronary occlusion

Chapter 2

Contemporary Overview and Clinical Perspectives of Chronic Total Occlusions

Loes P. Hoebers, Bimmer E. Claessen, George D. Dangas, Truls Råmunddal, Roxana Mehran, José P. S. Henriques

Nature Reviews Cardiology 2014 Aug;11(8):458-69

ABSTRACT

Chronic total occlusions (CTOs) are often detected on diagnostic coronary angiograms, but percutaneous coronary intervention (PCI) for CTO is currently infrequently performed owing to high technical difficulty, perceived risk of complications, and a lack of randomized data. However, successful CTO–PCI can significantly increase a patient's quality of life, improve left ventricular function, reduce the need for subsequent CABG surgery, and possibly improve long-term survival. A number of factors must be taken into account for the selection of patients for CTO–PCI, including the extent of ischaemia surrounding the occlusion, the level of myocardial viability, coronary location of the CTO, and probability of procedural success. Moreover, in patients with ST-segment elevation myocardial infarction, a CTO in a non-infarct-related artery might lead to an increase in infarct area, increased end-diastolic left ventricular pressure, and decreased left ventricular function, which are all associated with poor clinical outcomes. In this Review, we provide an overview of the anatomy and histopathology of CTOs, perceived benefits of CTO–PCI, considerations for patient selection for this procedure, and a summary of emerging techniques for CTO–PCI.

INTRODUCTION

Coronary artery disease (CAD) refers to atherosclerosis that might lead to narrowing of a coronary artery resulting in haemodynamically significant coronary lesions that induce ischaemia. Total coronary occlusions are coronary lesions that have become completely blocked. Over the past decade, remarkable progress has been achieved in the percutaneous management of CAD, such as the adoption of primary percutaneous coronary intervention (PCI) for acute myocardial infarction and the advent of drug-eluting stents (DESs).[1,2] Chronic total occlusions (CTOs) are often referred to as the final frontier for interventional cardiologists, who are often confronted with these complex lesions. The reported prevalence of CTOs varies widely from 16–50% in patients with clinically significant CAD, but is generally ~20% in large registries.[3-6] In a report from the Canadian multicentre CTO registry, a CTO was observed in 14.7% of patients without previous CABG surgery undergoing coronary angiography, and 18.4% in patients with clinically significant CAD.[4] In this registry, the majority of patients with a CTO underwent medical treatment (64%) or were referred for CABG surgery (26%)—only 10% were referred for CTO–PCI revascularization.[4] The disparity between the high prevalence of CTOs and the low rate of invasive treatment emphasizes the higher technical difficulty and perceived risk of complications compared with noninvasive treatment, but also the clinical uncertainties with regard to which patients benefit from CTO revascularization.[4,7] In this Review, we aim to provide an overview of the anatomy and histopathology of CTOs, patient and lesion characteristics, and patient selection criteria for CTO–PCI, with an emphasis on the current evidence regarding the clinical relevance and rationale of CTO–PCI.

CHARACTERISTICS OF CTOs

Definition

A uniform definition is essential for comparing the results of different studies. Consequently, a consensus document was published in 2005 in which a definition for CTOs was proposed.[8] A 'true' CTO arises owing to complete interruption of coronary flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0), whereas occlusions with minimal contrast penetration through the lesion without distal-vessel opacification (TIMI 1 flow) are classed as a 'functional' CTO. However, in the literature, the distinction between true and functional CTOs is rarely taken into consideration.[8] To be classed as a CTO, the lesion must have been present for ≥3 months. However, the period of time for which a CTO has been present is difficult to ascertain with complete certainty and, therefore, the age of

the occlusion is often determined after careful assessment of a patient's medical history and cardiac symptoms in the previous 3 months.[8]

Before PCI was regularly used to treat acute myocardial infarction, a CTO could evolve after such an event in 30% of patients who received thrombolytic treatment, and in 45% of those who did not receive pharmacological reperfusion therapy.[8-10] These rates have now dropped because of PCI, but a CTO might still develop after a failed intervention or subsequent vessel reocclusion in 5–10% of patients who have had a myocardial infarction.[11,12] However, the majority (~60%) of patients with a CTO do not have a history of myocardial infarction,[4] suggesting that an alternative mechanism can also lead to CTO. For example, the recruitment of collateral vessels to counterbalance the gradual progression to an occluded artery might limit myocardial damage resulting in the absence of, or only mild, clinical symptoms.[13]

Histopathology

In a post-mortem study of 61 patients in whom a CTO was identified on angiography in the 3 months before death (96 lesions in total), the thrombotic occlusion progressed over time from a 'soft' to a 'hard' lesion composition.[14] Soft plaques are composed of foam cells and cells with a high cholesterol content, and dense fibrous tissue at the proximal and distal ends (proximal and distal cap) with loose fibrous tissue in between.[14] Hard intimal plaques are characterized by calcification. The severity and extent of calcification increases with the duration of CTO, but is even present in 54% of occlusions <3 months old.[14] Nevertheless, with advancing CTO age, the calcium and collagen content of the intimal plaque increases.[14,15] Collagen is also a predominant component at the proximal fibrous cap and acts as an occlusive barrier.[16] This observation might partly explain the incremental procedural difficulty with advancing age of the occlusion, and the high procedural failure rate (15–32%) compared with that for nonocclusive lesions (~3%).[17,18]

Within CTO lesions, microchannels with an average diameter of 200 μm are often observed (Figure 1),[14] which might facilitate lesion crossing during CTO–PCI. In an animal study in which the timing and type of microvessel formation were evaluated in a rabbit model of total occlusion, two types of microvessels were observed: circumferentially oriented (extravascular) and longitudinally oriented (intravascular) microvessels.[19] In this study, extravascular microvessels grew to a maximum size by 2 weeks and then progressively decreased over time with very minimal microvessels evident beyond 12 weeks. By contrast, intravascular microvessel formation developed more slowly, with peak vascular volume at 6 weeks and was more prominent in the body compared with the proximal and distal ends of the CTO, probably owing to increased hypoxia. Channels that link extravascular and intravascular channels were observed at all time points. When the occlusion was 6 weeks old, intravascular neovascularization also occurred at both the proximal and distal ends of the lesion. As the occlusion further aged, only

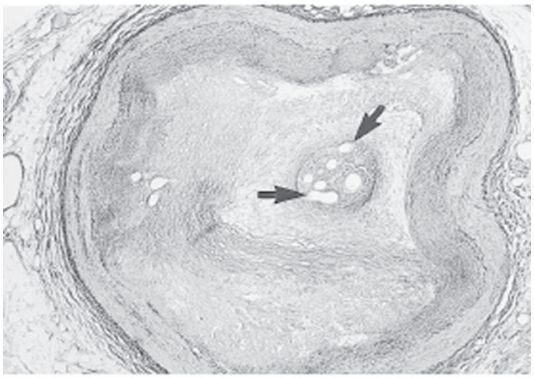

Figure 1. Chronic total occlusion demonstrating lumen recanalization with small and intermediate neovascular channels (arrows). Permission obtained from Srivatsa, S. S. *et al.* Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J. Am. Coll. Cardiol.* 29, 955–963 © Elsevier (1997).

a single narrow intravascular channel with a small and tortuous pathway was present in 85% of lesions.[19] This observed temporal and geographical pattern of microvessel formation and the presence of connecting microvessels implies that the extravascular vessels might initiate formation of the intravascular channels within the centre of the occlusion.[19] The intravascular and extravascular communicating channels exit the lesion at an angle close to 90° to the path of the artery, which could be responsible for the often-observed diversion of guidewires into the extravascular space.[20,21] Post-mortem studies in humans support this mechanism—microchannels mostly lead into the adventitia, small side branches, or vaso vasorum; however, they might also extend from the proximal to the distal lumen.[14,20] Unfortunately, insufficient data from human CTO studies exist to confirm whether intravascular channels are actually initiated by extravascular channels. Other mechanisms might also be involved. The origin for neoangiogenesis within the CTO could be from the proximal and distal nonoccluded ends, or driven by the circulating endothelial progenitor cells, as reported in venous thrombi.[22] Extravascular channels might already be present and could, therefore, develop more easily than intravascular channels.

CLINICAL CHARACTERISTICS OF CTO

In general, CAD is more prevalent in men than women. A total of 70% of patients with CAD without a CTO are men, a figure that rises to 80% for those with CAD and a CTO.[4] In patients receiving CTO–PCI, women tend to be older, have hypertension and diabetes mellitus, and are less likely smokers, compared with male patients.[23] Moreover, female

patients with a CTO are less likely to have multivessel disease and more often have a CTO located in the left anterior descending (LAD) coronary artery (although with a shorter CTO length and fewer blunt stumps and bridging collaterals).[23] However, after multivariable adjustment for known predictors, sex was not associated with CTO–PCI failure.[23]

CTOs are most often observed in patients with a mean age of 66 ± 11 years, whereas patients with CAD but no CTO have a mean age of 64 ± 12 years.[4] Patients with a CTO have an increased cardiac risk profile compared with those with no CTO on their coronary angiogram, including a higher prevalence of diabetes mellitus (34% versus 26%), hypertension (75% versus 68%), hyperlipidaemia (82% versus 78%), heart failure (12% versus 9%), and peripheral artery disease (8% versus 4%).[4] Approximately 40% of patients with a CTO had a previous myocardial infarction, which is twice as high as in patients without a CTO.[4] Pathological Q waves indicative of myocardial infarction on an electrocardiogram correspond to the CTO territory in 32% of all CTOs in the right coronary artery (RCA), 13% in the LAD coronary artery, and 26% in left circumflex branch (LCx).[4] However, in an imaging study, the frequency of previous myocardial infarction was strikingly different based on clinical versus imaging criteria.[24] On electrocardiograms, Q waves were present in 25% of patients, 42% had experienced ischaemic symptoms consistent with myocardial infarction, whereas 86% of all patients had some evidence of scar tissue visualized by contrast-enhanced MRI.[24] The extent of transmural infarction in these patients was not reported. In the majority of the patients, the CTO was located in the RCA (47%), with the others in the LAD artery (20%), LCx artery (16%), or multiple locations (17%).[4]

BENEFITS OF CTO–PCI

Successful CTO revascularization is associated with improved clinical outcomes for patients, and several retrospective studies have shown various beneficial effects (Table 1). Improvements in angina and quality of life,[25] a potential improvement in electrical myocardial stability,[26,27] a reduced need for CABG surgery,[28] enhanced tolerance of future coronary events, increased left ventricular function,[29-34] and a substantial increase in survival[25,28,34-58] have all been associated with successful CTO revascularization procedures.

A major limitation of studies designed to evaluate clinical outcomes after CTO–PCI is selection bias, which is inherent in observational research. To date, no randomized trial has been conducted to evaluate the effect of CTO–PCI on clinical outcomes. All data on clinical outcome after CTO–PCI are from registries of patients who have an indication for CTO revascularization, where a comparison is made between successful and failed PCI.[25,28,34-58] These nonrandomized studies do not include a control group of patients with CTO lesions being treated with optimal medical therapy alone.[25,28,34-58] Evidence from randomized trials is needed to confirm whether CTO revascularization is, indeed,

Table 1. Positive effects of CTO revascularization.

Effect	Measure	Outcome
Improved survival[28]	Risk ratio (95%CI)	0.54 (0.45-0.65)
Improved LVEF[29-34]	Change in LVEF (%)	~4.0–4.5%
Improved health status[25]		
Symptom reduction	Change in SAQ score (SD)	14.8 (20.4)
Physical limitation	Change in SAQ score (SD)	17.3 (20.7)
Quality of life	Change in SAQ score (SD)	30.3 (23.1)
Ischaemic burden reduction[80]	Amount of ischaemic myocardium (%)	6.2
Fewer future cardiovascular events		
CABG surgery[28]	Risk ratio (95%CI)	0.25 (0.21–0.30)

Abbreviations: CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; SAQ, Seattle Angina Questionnaire.

associated with improved clinical outcome, or whether the perceived benefit of successful CTO–PCI results from complications related to procedural failure or comorbidities that reduce survival in the failed CTO–PCI group. Given that the mortality curves for successful and failed CTO–PCI diverge over time, procedural complications (which would manifest as a parting of the curves during the first week after the procedure with a parallel continuum) are unlikely to be contributory factors.[25,28,34-58] However, future randomized, controlled trials will provide the definite answer.

Myocardial viability

Myocardial viability is likely to be needed to improve left ventricular wall motion and function.[31,59] Several studies have shown an improvement in left ventricular ejection fraction (LVEF) after successful CTO revascularization.[29-34] The expected improvement or recovery of left ventricular function declines with the extent of nonviable myocardium, which correlates with the extent of infarction.[59] The effect of CTO–PCI ($n = 17$) versus medical treatment only ($n = 30$) on LVEF was compared using MRI in patients with nonviable myocardium.[60] Despite the lack of myocardial viability in these patients, local left ventricular wall motion and function improved at 6 months after PCI compared with preprocedural levels (LVEF +1.9 percentage points, SD 12.1), with a minimal increase in left ventricular end-diastolic volume (+3.0 ml, SD 34.6). Conversely, in patients who received only medical therapy, LVEF decreased (–3.7 percentage points, SD 11.5), with a substantial increase in left ventricular end-diastolic volume (+8.0 ml, SD 25.8), which indicates negative remodelling.[60] In 2011, the Surgical Treatment of Ischemic Heart Failure (STICH) investigators reported a prespecified substudy evaluating the interaction between myocardial viability and survival in 601 patients with ischaemic heart failure who were randomly assigned to CABG surgery or optimal medical therapy.[61] After cor-

rection of other prognostic variables, the presence of myocardial viability was no longer significantly associated with mortality ($P = 0.21$). However, the cohort sizes were not powered to detect differences in mortality, which was much lower in those with viable myocardium (37% versus 51% with ischaemic heart failure who were randomly assigned to CABG surgery or optimal medical therapy).[61] Myocardial viability and treatment assignment did not have a significant interaction with respect to mortality. These findings bring into question whether LVEF recovery is completely dependent on myocardial viability, but might support the electrical or the 'reserve' hypothesis. In this hypothesis, CTO patients might be more prone to future cardiovascular events and have less reserve, especially during an acute occlusion in one of the remaining coronary arteries.

Ischaemic burden

The expected beneficial prognostic effect of CTO revascularization is thought to be associated with the amount of ischaemic myocardium, as has been observed in patients with CAD in general.[62-64] CTO–PCI might be beneficial in the absence of ischaemia. In one study, patients with successful CTO–PCI of the LAD coronary artery ($n = 99$) were stratified according to the presence of perfusion defects on nuclear imaging before the procedure.[33] Both those with reversible ($n = 40$) and those with fixed ($n = 50$) perfusion defects had significant improvement at 1 year in perfusion abnormalities (–20%, $P = 0.001$ and –15%, $P = 0.041$, respectively), LVEF (6%, $P = 0.002$ and 4.1%, $P = 0{,}006$), quality of life measured as improved 6 min walking distance (~50 m, $P < 0.05$ and ~25 m, $P < 0.05$), and frequency of angina measured with the Seattle Angina Questionnaire (18, $P < 0.05$ and 15, $P < 0.05$). No benefit of CTO–PCI was observed in patients who had no perfusion defects ($n = 9$).[33] Adequately powered, randomized, controlled trials are needed to address the question of whether viable and ischaemic myocardium is required for improvement of clinical outcome.

Myocardial electrical stability

Currently, no evidence is available to show that myocardial electrical stability is improved after successful CTO–PCI. However, in patients with an implantable cardioverter–defibrillator (ICD) for ischaemic cardiomyopathy ($n = 162$), a CTO was significantly associated with ventricular arrhythmias requiring ICD therapy (HR 3.5, 95% CI 1.5–8.3, $P = 0.003$).[26] Two previously established arrhythmogenic factors might be responsible for the ventricular tachycardia: ischaemia owing to inadequate perfusion of the myocardium can lead to abnormal automaticity of the ventricular myocardial cells, and re-entry circuits in patients with a previous myocardial infarction and fibrous tissue interspersed with islands of viable tissue.[65] Restoring antegrade flow after successful CTO–PCI could resolve the ischaemia and might, therefore, enhance electrical stability in patients with

ventricular arrhythmia, regardless of the presence of an ICD, which only treats the arrhythmic defect and not the cause of ischaemia.

PATIENT SELECTION FOR CTO

Symptoms

In patients with a CTO, the presence of cardiac symptoms—despite optimal medical therapy—is an indication for CTO recanalization. In a study of 125 patients undergoing CTO–PCI, changes in health status outcomes between baseline and 1 month after the procedure were assessed using the Seattle Angina Questionnaire.[25] Significant improvements were observed in symptoms (15 ± 20, P <0.01), physical function (17 ± 21, P <0.01), and quality of life (30 ± 23, P <0.01), but mainly in those patients who were symptomatic. Notably, in our own experience, patients with a CTO often complain about exertional dyspnoea rather than typical chest pain.

Collateral circulation

Collateral circulation is a natural bypass system providing retrograde flow to the myocardial perfusion area of the CTO, which can be visualized on an angiogram (Figure 2). In individuals with haemodynamically significant atherosclerotic lesions, well-developed collateral arteries are present in ~35% of patients.[66,67] Collateral vessels develop from pre-existing interarterial anastomoses owing to a pressure gradient generated when a vessel narrows or is occluded,[68,69] and might limit myocardial damage and maintain myocardial viability in patients with a CTO.[13] However, because the recruitment is based on a pressure gradient across the occluded lesion, the presence of collateral circulation does not guarantee myocardial viability.[70] Conversely, well-developed collateral vessels are inversely correlated with the degree of transmural myocardial injury measured on contrast-enhanced MRI.[24] In a small study of 42 patients with 78 total occlusions, absent collateral vessels on angiography did not necessarily indicate a low probability of myocardial viability,[71] suggesting that regional myocardial perfusion (determined by PET) was sufficient to maintain viable myocardium.[71] This finding might be due to a limitation of angiographic assessment of collateral flow. Only channels >100–200 μm in diameter can be visualized with this technique, but many collateral vessels are smaller than this size.[14]

In >90% of patients with a CTO where collateral vessels provide adequate flow to maintain myocardial viability, the flow is insufficient to maintain adequate perfusion during pharmacological-induced stress, resulting in ischaemia.[72,73] Moreover, in approximately one-third of patients, the collateral supply is further reduced by coronary steal of the donor artery, defined as a drop in collateral coronary flow velocity reserve <0.85.[72,73]

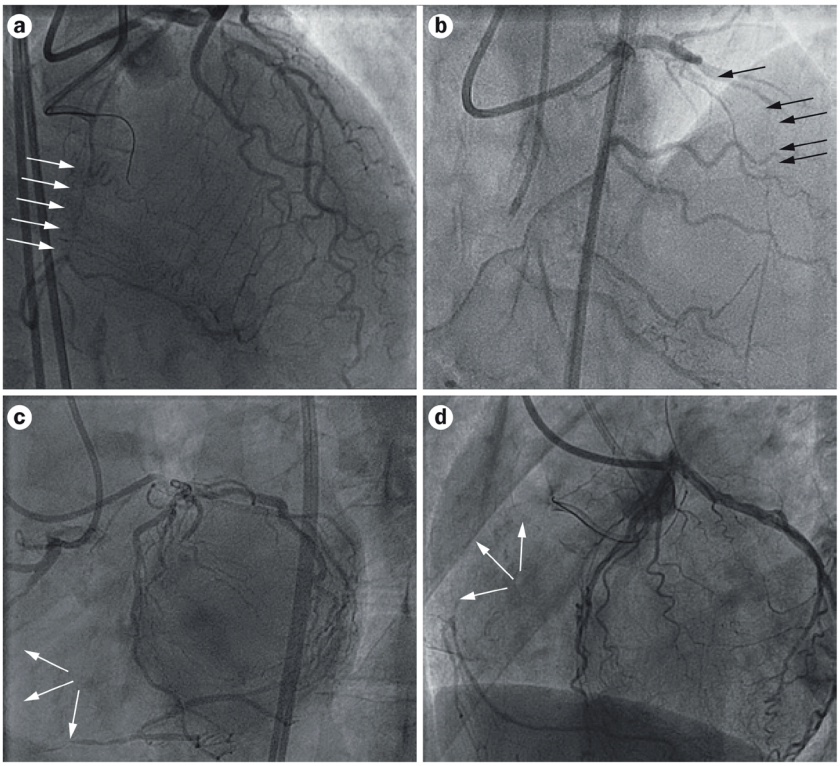

Figure 2. Chronic total occlusions with well-developed collateral circulation from the contralateral coronary system. a: CTO of the RCA, which receives retrograde flow from septal collateral arteries. b: CTO of the left anterior descending coronary artery, which receives retrograde flow from the RCA through septal collateral vessels. c: CTO of the RCA with epicardial collateral vessels from the left coronary system. d: CTO of the RCA with epicardial collateral vessels from the left coronary system. Abbreviations: CTO, chronic total occlusion; RCA, right coronary artery.

Consequently, the presence of collaterals in patients with CTOs is related neither to the extent of preserved left ventricular function, nor recovery of left ventricular function after successful CTO–PCI.[73] The presence of well-developed collateral vessels in symptomatic patients should not, therefore, be a reason to withhold CTO revascularization.

Ischaemic burden

Ischaemia is intrinsically linked to myocardial viability, and each factor must be interpreted in the context of the other. If ischaemia can be demonstrated by cardiac symptoms or stress testing, one can assume the associated myocardium is viable because a patient cannot experience symptoms or ischaemia from dead tissue. However, in patients with additional non-CTO lesions, establishing the lesion that is responsible for the symptoms and ischaemia is important.[74,75] The majority of patients with a CTO

and collateral circulation experience ischaemia during exercise owing to inadequate perfusion distally of the occlusion, often resulting in cardiac symptoms.[72,73] However, an additional mechanism that might also contribute to ischaemic burden has also been proposed.[76] Immediately after successful CTO–PCI, the coronary segments distal to the occlusion have been shown to be severely dysfunctional to regulatory feedback mechanisms of acetylcholine and nitrate challenges. Also, an intense vasoconstrictive reaction in response to acetylcholine was observed.[76] A damaged or dysfunctional endothelium has been shown to be an initiator of vascular atherosclerosis and is a predictor of coronary events in patients with CAD.[77,78] The pathophysiological explanation for this finding is still unknown, and further research is needed to investigate whether these effects are sustained or reversible over time.

In patients without cardiac symptoms and definite ischaemia in the area of CTO, testing of myocardial viability is required before considering CTO–PCI, because ischaemia can be present only when the myocardium is still viable. Ischaemia is often assessed as the degree of perfusion defect in stress versus rest: in the absence of perfusion defects, no ischaemia exists; reversible perfusion defects indicate ischaemia; whereas a fixed perfusion defect is most likely caused by scar tissue.[79] However, perfusion can be normal in nonviable myocardial areas after successful, but late, reperfusion treatment for an acute myocardial infarction, which can be evaluated using contrast-enhanced MRI.[31] Determining the extent of ischaemia that needs to be present to expect a beneficial effect of revascularization is difficult, especially in the absence of angina, because alleviation of symptoms is a valid reason for CTO–PCI. In asymptomatic patients, the achievable beneficial effects are improvement in physical activity, left ventricular function, electrical stability, and survival, and a reduced need for CABG surgery. In one study of 301 patients who underwent CTO–PCI, the level of ischaemia was assessed using serial myocardial perfusion imaging 12 ± 3 months before, and 12 ± 3 months after, the procedure.[80] Ischaemia was calculated using the difference between the summed stress and rest scores and converted to percentage of ischaemic myocardium. A meaningful improvement was defined as ≥5% decrease in ischaemic myocardium, because a change of this magnitude is known to be associated with reduced risk of death or myocardial infarction in patients with CAD.[64] In this cohort, the mean ischaemic burden decreased from 13.1 ± 11.9% at baseline to 6.9 ± 6.5% at follow-up after CTO–PCI. [80] Receiver operating characteristic analysis showed that 12.5% ischaemic burden at baseline was an optimal threshold to identify patients who would benefit from CTO–PCI in terms of a reduced ischaemic burden. Patients with a baseline ischaemic burden <6.25% were likely to have an increased ischaemic burden after PCI. Therefore, in asymptomatic patients with CTO, the ischaemic burden should be evaluated before CTO–PCI is considered.[64] In our opinion, a threshold of 12.5% can be used as a reference, but larger, prospective studies are needed to set a definitive cut-off value.

Myocardial viability

The presence and magnitude of myocardial viability is important to identify patients who might most benefit from CTO–PCI. A combination of viability parameters can predict improvement of myocardial function with more accuracy than the use of a single parameter including: dobutamine contractile reserve; transmural extent of infarction; and segmental wall thickening of normal remaining myocardium on cardiac MRI, especially in segments with intermediate extent of infarction.[31] Contractile reserve assessed with dobutamine seems to be one of the best predictors of myocardial improvement, because it directly unmasks the potential presence of contractile reserve in dysfunctional, noninfarcted myocardium.[81-85] Although intuitively logical, evidence that myocardial viability is absolutely necessary is limited and inconsistent. However, until an adequately powered, randomized clinical trial shows otherwise, the presence of myocardial viability is required to justify CTO–PCI.

Location of CTO

The location of a CTO in the coronary tree can be important for patient survival. In a study of 2,608 patients, successful versus failed CTO–PCI was beneficial only in patients with a CTO in the LAD artery (88.9% versus 80.2%; $P < 0.001$), but not in those with a CTO in the LCx artery (86.1% versus 82.1%; $P = 0.21$), or RCA (87.7% versus 84.9%; $P = 0.23$) at 5 year follow-up.[86] However, these results might be influenced by an unconventional definition of procedural success—angiographic success with no in-hospital major adverse cardiac event (that is death, myocardial infarction with new Q waves on the electrocardiogram, or urgent target-vessel revascularization).[86] Consequently, all in-hospital deaths were considered procedural failures. From our own evaluation of the Kaplan–Meier curves of patients with a CTO in the LAD artery, the mortality difference seems to be determined in the first week, after which the slopes of the successful and failed curves seem similar.

However, data from another large, multinational registry with 1,734 patients with CTO showed a survival benefit after successful CTO–PCI in either the LAD or the LCx arteries, but not in the RCA. At 5 years, mortality for successful versus failed CTO–PCI was 6.7% versus 11.0% in the LAD artery ($P = 0.03$), 5.5% versus 13.9% in the LCx artery ($P = 0.01$), and 6.6% versus 4.1% in the RCA ($P = 0.80$).[87] Two potential explanations might account for this finding. First, the region of the myocardium supplied by the LAD artery is greater than the RCA or LCx territory; the effect of CTO–PCI in the LAD artery might, therefore, be more easily demonstrated. Secondly, sympathetic innervation is more pronounced in the anterior than in the inferior myocardial wall—vagal afferent receptors have a preferential distribution on the posterior wall of the left ventricle.[88,89] In the clinical setting, inferior myocardial infarction often leads to vagal activation.[88,89] Alterations in the balance of the autonomic nervous system owing to coronary occlusion has also been associated with life threatening ventricular arrhythmias and cardiac death in survivors

of myocardial infarction.[90] In animal experiments, vagal stimulation or sympathetic inhibition reduces the threshold for ventricular fibrillation.[91] Therefore, patients with an inferior occlusion after myocardial infarction might be relatively protected from ventricular fibrillation, whereas patients with an anterior occlusion might have a higher frequency of ventricular arrhythmia. In a small cohort ($n = 23$), CTO–PCI had a beneficial effect on the autonomic nervous system in the LAD artery, which was not observed after CTO–PCI of the RCA.[92] These findings suggest a potential antiarrhythmic effect after LAD revascularization, resulting from a shift in the autonomic balance in favour of the parasympathetic nervous system.

Until a randomized trial shows otherwise, all CTO locations should be evaluated for revascularization. However, data suggest that prognostic variability might be present. Consequently, in our opinion, revascularization of a CTO located in the LAD artery (and possibly the LCx artery) is highly recommended.

CTO IN PATIENTS WITH STEMI

In the past decade, several papers have highlighted the importance of a concurrent CTO in patients with ST-segment elevation myocardial infarction (STEMI) who receive primary PCI.[93-96] A CTO in a noninfarct-related artery is present in approximately 10% of all patients with STEMI.[93,95] The presence of a CTO in a noninfarct-related artery in patients with multiple-vessel disease seems to explain to a large extent the adverse prognosis (compared with those patients with single-vessel disease) in these individuals (Figure 3). Patients with a CTO in a noninfarct-related artery have a high prevalence of cardiovascular risk factors and comorbidities compared with those with no CTO.[93-96] In addition, patients with STEMI and a CTO often have a higher increase in the level of cardiac enzymes than those without a CTO, which is indicative of a larger infarct size.[93,95] Interarterial connections between the CTO and infarct-related artery through collateral vessels might increase the endangered myocardial area after acute closure of the culprit artery, because both its own supply and the myocardium served by that artery is at risk, leading to larger infarct size, increased end-diastolic left ventricular pressure, and suboptimal epicardial and myocardial reperfusion.[94,95] In substudies from the TAPAS and HORIZONS-AMI trials, the presence of a CTO in a noninfarct-related artery was associated with incomplete ST-segment resolution, lower myocardial blush grades, and lower post-procedural TIMI flow grades in the culprit artery (Figure 4).[95]

A distinction has also been made between patients with STEMI and the presence or absence of cardiogenic shock.[97] In patients with STEMI and multivessel disease who are not in cardiogenic shock, a coexisting CTO in a noninfarct-related artery is a predictor of both early and late mortality.[97] In patients with cardiogenic shock, multivessel with

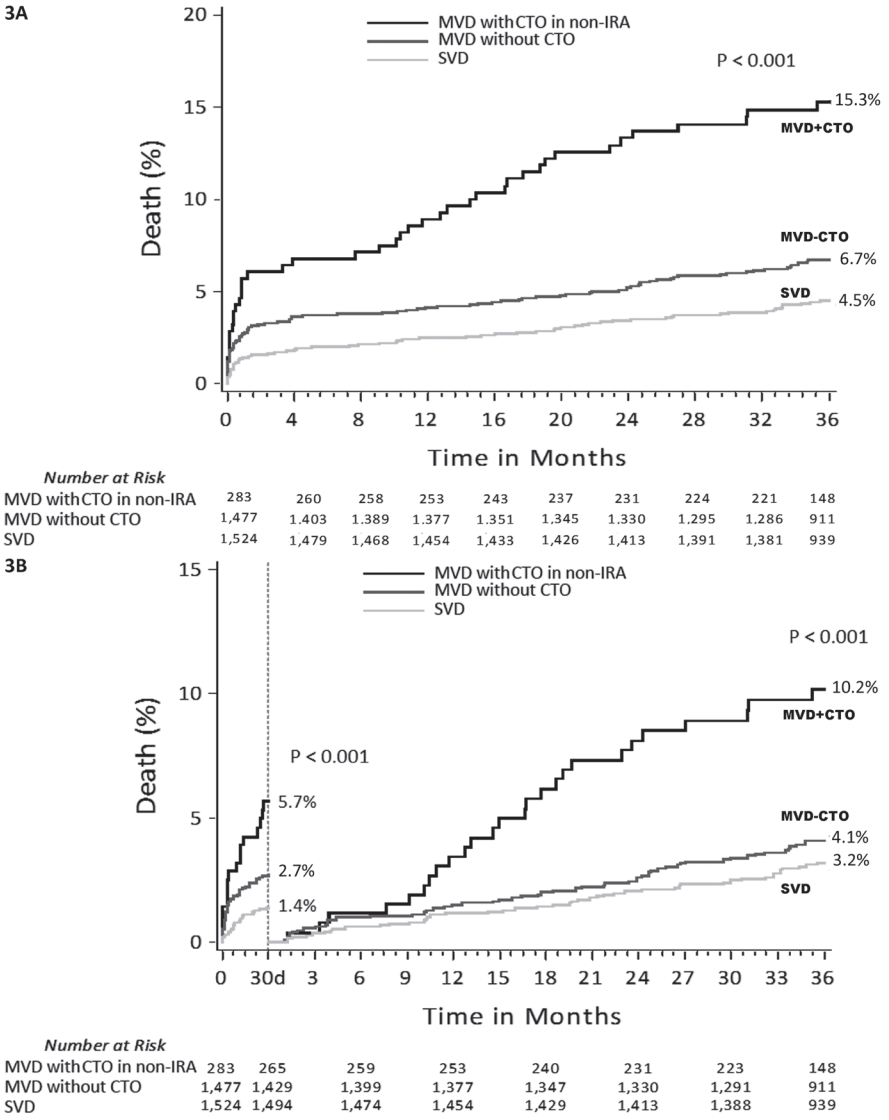

Figure 3. Time-to-event curves for all-cause mortality in patients with SVD, MVD without a CTO, or MVD with a CTO in a non-IRA. a: Mortality at 3 years. b: Mortality between 0 and 30 days, and 30 days and 3 years. Abbreviations: CTO, chronic total occlusion; IRA, infarct-related artery; MVD, multivessel disease; SVD, single-vessel disease. Permission obtained from Oxford University Press, Claessen, B. E. *et al.* Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur. Heart J.* 33, 768–775 (2012).

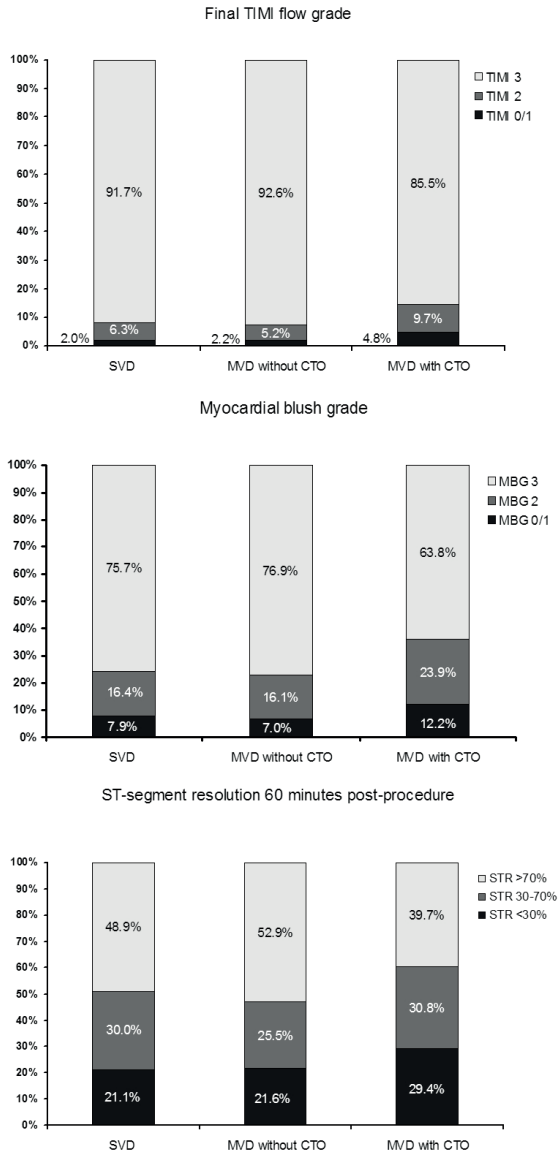

Figure 4. Markers of reperfusion in patients with SVD, MVD without a CTO, or MVD with a CTO. Abbreviations: CTO, chronic total occlusion; MBG, myocardial blush grade; MVD, multivessel disease; STR, ST-segment resolution; SVD, single-vessel disease; TIMI, Thrombolysis In Myocardial Infarction.

or without a CTO was a predictor of short-term mortality.[97] However, for long-term mortality, only the presence of a CTO seemed to be of importance. In our opinion, this observation might be explained by the reduced cardiac output and coronary blood flow in patients with cardiogenic shock, which might increase the functional importance of nonocclusive multivessel lesions, resulting in myocardial ischaemia in perfusion areas other than that of the culprit lesion.

The association between a noninfarct-related CTO and impaired outcome has also been reported in patients with non-STEMI.[98,99] However, whether a CTO is just an indicator of adverse prognosis, or whether additional CTO–PCI revascularization after a primary PCI for STEMI can improve clinical outcome remains unknown.

CTO AND FUTURE ADVERSE EVENTS

A CTO might increase the risk of future adverse cardiac events in another artery, especially in the setting of an acute myocardial infarction where only one coronary artery remains for blood supply. An artery with a CTO is unable to donate collateral vessels, which is normally associated with a reduction in infarct size, improved left ventricular function, and increased survival.[13,66,100] Conversely, when the myocardium of the CTO territory is dependent on collateral circulation of a remaining coronary artery, in theory, the amount of myocardium at risk after acute occlusion of the donor artery will extend beyond its own perfusion area, with an increased infarct size, major left ventricular dysfunction, heart failure, and even increased mortality. Consequently, patients with STEMI and a CTO in a noninfarct-related artery more often develop cardiogenic shock upon presentation to the catheterization laboratory than patients without a CTO.[97] This reduced myocardial reserve or lack of a collateral circulation 'back-up' system during a new coronary event might be another reason for a patient to undergo CTO–PCI revascularization. However, to test this hypothesis in a clinical trial would be extremely difficult owing to the very large number of patients required, and the need for extensive follow-up (>5 years).

In individuals without acute myocardial infarction, the presence of a CTO in the RCA was shown to be an independent predictor of mortality in patients ($n = 330$) undergoing unprotected left main PCI (HR 2.15, 95% CI 1.02–4.50, $P = 0.043$).[101] Furthermore, successful CTO–PCI has been shown to reduce the need for CABG surgery compared with failed CTO–PCI (risk ratio 0.25, 95% CI 0.21–0.30, $P < 0.001$).[28]

PROBABILITY OF SUCCESSFUL PCI

Despite procedural complexity, increased operator volumes have led to an improved success rate of CTO–PCI from approximately 68% to 85%.[17,102] This improvement is accompanied by a low risk of procedural complications, regardless of procedural success.[17,18,102,103] These figures are similar to non-CTO procedures, with the exception of a significantly increased fluoroscopy time and use of contrast agent (Table 2).[18] However, complication rates are significantly higher in patients with failed CTO–PCI than in those with a successful intervention (Table 3).[102]

Table 2. In-hospital complications of patients receiving PCI for CTO versus non-CTO lesions.

Complication	CTO	No CTO	P-value
Death (%)	0.3	0.2	0.35
Nonfatal myocardial infarction (%)	0.4	0.6	1.0
Stroke (%)	0.1	0.1	0.47
Resuscitation (%)	0.7	0.2	0.015
Others, for example, tamponade (%)	1.1	0.5	0.06
Emergency CABG surgery (%)	0	0.1	1.0
Median hospital stay days (quartile range)	2 (1–5)	2 (1–4)	0.72

Abbreviations: CTO, chronic total occlusion; PCI, percutaneous coronary intervention. Permission obtained from Werner, G. S. *et al.*, Contemporary success and complication rates of percutaneous coronary intervention for chronic total coronary occlusions: results from the ALKK quality control registry of 2006. *EuroIntervention* 6, 361–366 © Europa (2010).

Table 3 . Complications in patients with CTO–PCI.[102]

Procedural complication (%)	Successful CTO-PCI	Failed CTO-PCI	P-value
Death	0.4	1.5	<0.0001
Stroke	0.07	0.4	0.04
Coronary perforation	3.7	10.7	<0.0001
Tamponade	0.0	1.7	<0.0001

Abbreviations: CTO, chronic total occlusion; PCI, percutaneous coronary intervention

Several factors might increase procedural complexity and limit successful outcome. A number of angiographic features have been associated with a reduced success rate of CTO–PCI: increasing age of the CTO, presence of a blunt stump, presence of bridging collaterals, presence of calcium, excessive tortuosity, long occlusion length, and side branches at the occlusion entry.[51,52,104,105] The majority of these features are captured in the J-CTO (multicentre CTO registry in Japan) score (Table 4). This score was determined by assigning one point for each independent predictor of crossing the CTO lesion within

Table 4. J-CTO score for predicting successful guidewire crossing within 30 min.

Variables	OR (95% CI)	β coefficient	Point
Previously failed lesion	0.39 (0.15–0.97)	0.93	1
Blunt stump type	0.32 (0.18–0.55)	1.14	1
Bending	0.34 (0.20–0.58)	1.09	1
Calcification	0.26 (0.15–0.44)	1.36	1
Occlusion length ≥20 mm	0.19 (0.09–0.39)	1.65	1

Abbreviations: J-CTO, multicentre CTO registry in Japan. Permission obtained from Morino, Y. *et al.* Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc. Interv.* 4, 213–221 © Elsevier (2011).

30 min of starting the procedure.[106] The summed value was then used to develop a model stratifying all lesions into four groups indicating the difficulty of the procedure: easy (score = 0); intermediate (score = 1); difficult (score = 2); and very difficult (score = 3–5). In our opinion, a high J-CTO score does not mean that no PCI attempt should be made, but might indicate whether a patient should be referred to an experienced centre or for CABG surgery, because operator experience determines successful outcome.

TREATMENT AFTER CTO–PCI

Historically, CTO–PCI has been associated with a high rate of restenosis and reocclusion[1,107-109] therefore, the implantation of a DES is recommended during a successful procedure.[110] The introduction of bare-metal stents (BMS) in the 1990s led to a significant reduction in the need for repeat revascularization compared with balloon angioplasty alone.[107,109,111] In the first decade of the 21st century, DES led to an incremental 60% reduction in the relative risk of repeat revascularization after CTO–PCI.[1] The risk of stent thrombosis tends to be higher with DES compared with BMS (relative risk 2.79, 95% CI 0.98–7.97, $P = 0.06$).[1] However, investigators from a multinational CTO registry reported similar rates of stent thrombosis with BMS or DES in a cohort of 1,160 patients up to 5 years after successful CTO–PCI (2.3% versus 1.7%; $P = 0.58$).[49,108] Only a small number of randomized trials have been conducted to investigate the safety and efficacy of various types of DES; therefore, no recommendations can be made specifying which DES should be used.[112-116] To date, no information is available about the performance of bioabsorbable stents in CTO lesions. The resorption of bioabsorbable scaffolds has been hypothesized to enable full restoration of vasomotion and autoregulation in the CTO territory.[117] The patency rate after CTO–PCI at 6–9 month follow-up is approximately 90% for first-generation DES, and 97% for everolimus-eluting stents.[118] The rate of 1-year graft

patency in patients with a CTO is 80% for saphenous vein grafts, and 99% for internal mammary artery grafts.[119]

FORTHCOMING CTO TRIALS

Investigators in the EXPLORE trial[120] will evaluate whether CTO–PCI in a noninfarct-related artery within 7 days of primary PCI can improve LVEF and reduce left ventricular end-diastolic volume, compared with optimal medical therapy. The trail rationale is based on the assumptions that recanalization of the CTO will restore contractile function to the myocardium and might improve the healing of the infarct border zone, protect against negative remodelling, and thereby preserve residual left ventricular function. Until a randomized controlled trial proves otherwise, subsequent CTO–PCI in the sub-acute setting after STEMI is not recommended in clinically stable patients. The EXPLORE trial is expected to complete enrolment in 2014. Investigators in two other randomized clinical trials powered for clinical end points are currently enrolling patients with CTO and stable CAD. Researcher in the EuroCTO trial[121] will randomly assign 1,200 patients to receive either PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is quality of life at 1 year and major cardiovascular events (a composite of all-cause death and nonfatal myocardial infarction) at 3 years. Similarly, investigators in the DECISION-CTO trial[122] will randomly assign 1,284 patients (in a 1:1 ratio) to receive PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is a composite of all-cause mortality, myocardial infarction, stroke, and any revascularization at 3-year follow-up.

EMERGING TREATMENTS FOR CTO

Technical improvements in microcatheters, which have enabled enhanced antegrade and retrograde support, and the development of dedicated guidewires for CTO have improved the success rate of CTO–PCI.[123] The success of CTO procedures is now >85% in centres with experienced interventional cardiologists and will probably improve further as technical developments continue.[123] 3D intravascular imaging with, for example, the forward-looking intravascular ultrasonography catheter, which enables a successful and safe crossing of the cap and occlusion, is a promising tool for CTO treatment.[124,125] Moreover, the CrossBoss™ catheter and Stingray™ devices (Boston Scientific, USA) can accurately target and re-enter the true lumen from a subintimal position, which is now incorporated in the 'hybrid' approach to CTO–PCI.[125,126] This approach focuses on open-

ing the occluded vessel using all feasible techniques (antegrade, retrograde, true-to-true lumen crossing or re-entry) in the safest, most effective, and most efficient way.

A novel approach has been developed for complex CTO lesions with previous failed percutaneous revascularization attempts, and has been shown to be safe in a first-in-man study.[127] In 20 patients, CTOs in which guidewire crossing failed were pretreated with intracoronary collagenase for 30 min. The following day, another attempt was made to cross the lesion, which was successful in 75% of patients. Therefore, preliminary results suggest that collagenase facilitates guidewire crossing and might be a useful tool for the antegrade approach in difficult procedures; however, procedural efficacy still needs to be evaluated.[127]

Other strategies to restore compensatory blood flow to the myocardial territory of a CTO—such as stimulation of collateral growth through arteriogenesis or external counterpulsation—might also be alternative approaches to CTO–PCI. A detailed discussion of these non-PCI strategies is beyond the scope of this Review, and has been discussed extensively elsewhere.[67,128-132]

CONCLUSIONS

In patients with clinically significant CAD, a CTO is frequently observed on angiography, but the uptake of CTO–PCI by cardiologists is low, which reflects the procedural complexity and lack of randomized data. However, these factors alone do not justify withholding PCI in patients with a CTO. Careful selection of patients can improve clinical outcome in these high-risk patients. In experienced centres, the success rate is up to 85%, without an increased risk of complications compared with non-CTO–PCI. Evidence from observational studies suggests that the beneficial effects of CTO–PCI will finally be extended by evidence from adequately powered, randomized, controlled trials within the next few years.

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Chapter 3

Chronic Total Occlusions in Sweden – A report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

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PLoS One. 2014 Aug;9(8)

ABSTRACT

Introduction

Evidence for the current guidelines for the treatment of patients with chronic total occlusions (CTO) in coronary arteries is limited. In this study we identified all CTO patients registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and studied the prevalence, patient characteristics and treatment decisions for CTO in Sweden.

Methods and Results

Between January 2005 and January 2012, 276,931 procedures [coronary angiography or percutaneous coronary intervention] were performed in 215,836 patients registered in SCAAR. Registry data were scrutinized for the presence of CTO, which was defined as 100% luminal diameter stenosis known or assumed to be ≥3 months old. After exclusion of patients with previous coronary artery bypass graft (CABG) surgery or coronary occlusions due to acute coronary syndrome, we identified 16,818 CTO patients. A CTO was observed in 10.9% of all coronary angiographies and in 16.0% of patients with coronary artery disease (CAD). The majority of CTO patients were treated conservatively and PCI of CTO accounted for only 5.8% of all PCI procedures. CTO patients with diabetes and multivessel disease were more likely to be referred to CABG.

Conclusion

CTO is a common finding in Swedish patients undergoing coronary angiography but the number of CTO procedures in Sweden is low. Patients with CTO are a high-risk subgroup of patients with coronary artery disease. SCAAR has the largest register of CTO patients and therefore may be valuable for studies of clinical importance of CTO and optimal treatment for CTO patients.

INTRODUCTION

Chronic total occlusions (CTO) are difficult to treat with percutaneous coronary intervention (PCI)[1]. Revascularization of CTO demands expert skills, longer procedural time and is associated with higher procedural risks such as coronary perforation, contrast nephropathy, radiation exposure, and loss of collateral circulation.[1,2] According to the European and American guidelines, PCI of CTO has class-IIa recommendation (weight of evidence in favour of the treatments usefulness/ efficacy)[3,4] but this recommendation is based on small retrospective studies and on expert consensus. The true prevalence of a CTO in the general population is unknown and few studies have addressed this question. In observational studies, a CTO was found in approximately one third of the patients referred for coronary angiography[5-7]. However, these studies were based on low number of patients and hospitals, and may therefore be prone to selection bias. To date, no epidemiological study has investigated the prevalence and clinical characteristics of CTO patients at the nationwide level. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) is a prospective national registry that collects data about all patient undergoing coronary angiography and PCI in Sweden[8]. Therefore, we identified all CTO patients registered in SCAAR and studied prevalence, patient characteristics and treatment decision for CTO in Sweden.

METHODS

Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

The SCAAR registry was established in 1999 after the unification of Swedish Coronary Angiography registry (Acta Coronaria) and the Swedish Coronary Angioplasty registry (SCAP). SCAAR, which is a part of the national SWEDEHEART registry, holds data on all consecutive patients from all centres that perform coronary angiography and PCI in Sweden. The registry is independent of commercial funding and is sponsored by the Swedish Health Authorities only. The technology has been developed and administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has been Internet-based, with recording of data online through an Internet interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Center. In total, there are 30 hospitals with cardiac catheterization facilities in Sweden of which 9 are university hospitals. In SCAAR, a coronary angiography procedure is described by approximately 50 variables while a PCI procedure allows for is described by approximately 200 variables. The information about clinical characteristics and procedural details is entered into the registry immediately after the procedure by the PCI physician after the review of clinical information.

Ethics statement

The study was approved by the regional ethical review board of Uppsala University, Uppsala,Sweden. The regional ethical review board waived the need for written informed consent from the participants according to Swedish legislation and because data were de-identified and anonymized before analysis.

Definitions

We defined CTO as 100% luminal diameter stenosis and the absence of antegrade flow known or assumed to be ≥3 months duration[6,9,10]. Coronary artery disease (CAD) was defined as a luminal narrowing ≥50% on angiography. Procedural success after PCI treatment of the coronary lesion is defined as residual stenosis < 50%, decreased grade of stenosis after intervention by at least 20%, normal blood flow and no serious complications.

Study cohort

We used two different methods to identify CTO patients in SCAAR between January 2005 and January 2012. The first method is based on the information about %-luminal stenosis at the level of coronary segments that was introduced in 2005. From this date onwards, the information derived from a diagnostic coronary angiogram can also be used to determine if a coronary segment was totally occluded. In order to differentiate between acute and chronic occlusions, we excluded patients who underwent a procedure for ACS in whom the occlusion was located in the same coronary artery as the culprit vessel. Furthermore, we excluded patients who underwent a procedure in the same vessel within the previous 3 months. The CTO patients identified by this method constitute the *coronary segment subcohort*. The second method is based on the separate variable by which PCI operators classify a treated occlusion either as a chronic occlusion ≥3 months duration or as an acute/subacute occlusion ≤3 months duration. The patients with previous coronary artery bypass graft (CABG) surgery were excluded from analysis as the patency of the graft could not be determined. The study was scrutinised and approved by the ethics board according to the Swedish law and regulations.

Total CTO cohort

The total CTO cohort contains all CTO patients identified by either of the two methods (Figure 1). Patients and procedures in which the same CTO lesion was registered through both methods or at multiple occasions were identified and duplicate observations were excluded from the analysis. For each patient, the procedure where the CTO was observed first was selected.

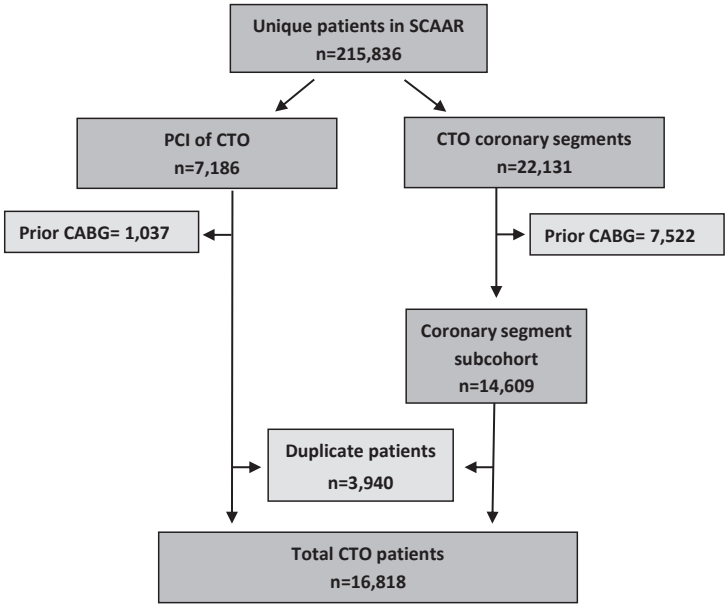

Figure 1. Flow chart for identification and selection of CTO patients in SCAAR.
Based on the selection methods we have defined two CTO groups. The first group - *the total CTO cohort*- contains all CTO patients recognized by one or both methods during the period. The second group is the subcohort that contains the patients in whom a CTO was identified through the %-luminal stenosis on the coronary segments – *the coronary segment subcohort.*

Coronary segment subcohort

We also present data from the subcohort of patients who were identified according to whether they had a 100% luminal stenosis and considered to be a CTO based on the above mentioned inclusion criteria. We compared patient characteristics and treatment decisions between patients with significant coronary artery disease in whom a CTO was observed or not. Prevalence of a CTO was calculated only from the coronary segment subcohort and in relation to three different denominators: the number of unique procedures, the number of unique patients and the number of unique patients with significant coronary artery disease.

Validation of CTO

Validation of the CTO definition was performed in a subgroup of 955 patients from one university hospital (Sahlgrenska University Hospital) and from three county hospitals (Norra Älvsborgs Hospital, Borås Hospital, Skövde Hospital). This subgroup represents 5.7% of all identified CTO patients in SCAAR in the study period. The patients were randomly selected by means of random number generator using Stata software (Version 12.1, StataCorp, College Station, Texas, USA). The validation procedure was conducted

by a panel consisting of five experienced interventional cardiologists. The panellists examined individual coronary angiograms according to a monitoring plan defined in advance. Each angiogram was evaluated in regard to whether the patient had previous CABG, whether the treated occlusion was ≥3 months old and whether 100% segmental stenosis on angiogram was an occlusion ≥3 months old. The results from the validation procedure were then compared to the data entered in SCAAR.

Statistical analysis

Differences in baseline characteristics between the groups were tested by the χ^2 test for categorical variables while Mann–Whitney U test and Kruskal-Wallis test were used for comparison of continuous non-normally distributed variables. We used Shapiro-Wilks test to test for normal distribution. Tests for trends were made using linear contrasts of means in a one-way analysis of variance model for numerical data and the Armitage-Cohrane trend test for categorical data. We used logistic regression with test for linear trend to evaluate whether annual incidence of CTO and success rate for PCI of CTO changed during the study period. Statistical significance was defined as a P-value <0.05. All analyses were performed using Stata software (Version 13.1, StataCorp, College Station, Texas, USA).

RESULTS

Prevalence of CTO in Sweden

As of January 2012, 497,572 procedures (coronary angiographies and PCIs) performed in 348,863 patients have been reported in SCAAR. The numbers of PCIs and coronary angiographies have been increasing since 1999 (Figure 2). The annual rate of PCIs for CTO remained low (~1200 in 2011). Since 2005, 276,931 procedures in 215,836 patients were performed in Sweden. The total number of CTO patients without previous CABG was 16,818 and constitutes the total CTO cohort (Figure 1). Information about age of the treated occlusion was missing in 0.8% (n=1077) of all PCI procedures. Of the 134,087 reported PCI procedures 7,816 (5.8%) involved the treatment of a CTO. These procedures were performed in 29 different hospitals on 7,186 unique patients of whom 6,149 without prior CABG. Almost half (43%) of all CTO procedures were performed at university hospitals. Data on procedural success was missing in 12 procedures (0.2%). The overall success rate was 53.1%. The annual success rate did not change significantly during the study period with 54.4% in 2005 and 56.6% in 2011 (P=0.15). Complete information about luminal %-stenosis in coronary segments was available in 160,159 (57.8%) angiographies of which 144,744 were performed in patients without previous CABG. A CTO was observed in 10.6% of these angiographies which were made in 126,745 patients. Of these patients,

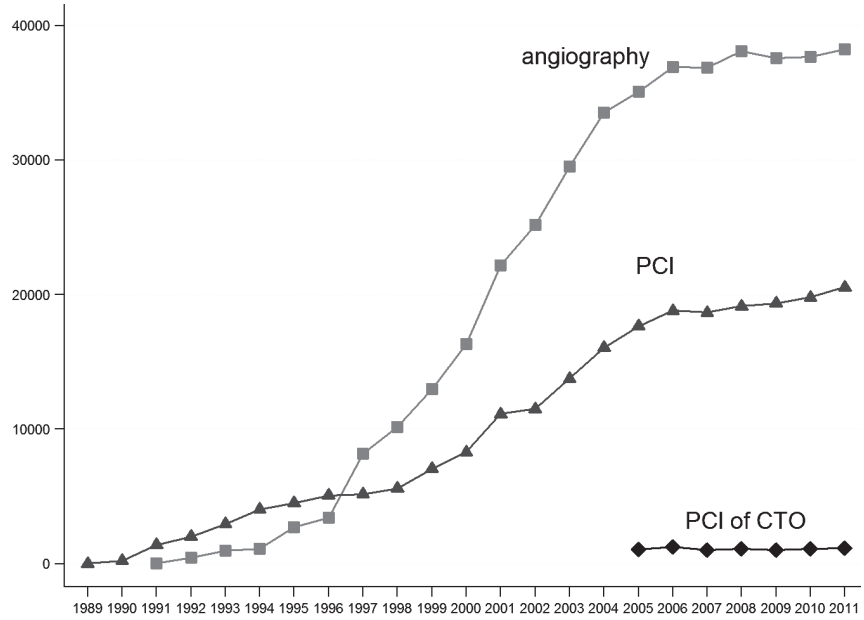

Figure 2. Annual number of coronary angiographies, PCI's, and PCI's performed in CTO patients in Sweden reported in SCAAR since 1999.

14,609 had at least one CTO resulting in a prevalence of 11.5%. CAD was diagnosed in 91,154 patients of which 16.0% had a CTO. In patients who underwent multiple procedures, the CTO was diagnosed on the first diagnostic angiogram in 90% of the cases. The annual number of diagnosed CTO in patients undergoing coronary angiography decreased gradually by 25% from 11.5% in 2005 to 8.6% in 2012 (OR 0.97;95% CI 0.96–0.98; P,0.001 test for linear trend). In patients with significant coronary artery disease, CTO decreased by 12% from 17.2% in 2005 to 15.1% in 2012 (OR 0.95; 95% CI 0.94–0.96; P<0.001 test for linear trend).

Patient characteristics

The clinical characteristics of all CTO patients - the total CTO cohort - registered in SCAAR since 2005 are summarized in Table 1. The majority of CTO patients were male. The high occurrence of previous MI (37%) and the presence of traditional cardiovascular risk factors make CTO patients a high-risk population. Table 2 shows the baseline demographic and angiographic characteristics of patients with CAD stratified for the presence of a CTO on angiography (coronary segment subcohort). CTO patients were more often males and were more likely to have risk factors including previous MI. In addition, the extent of CAD was more severe in CTO patients with more multivessel and left main disease. Although CTO was diagnosed in the majority of cases during a coronary angiography for

Table 1. Baseline characteristics of the total CTO cohort in SCAAR at the time of diagnosis based on data collected during the period 2005-2012.

	All CTO patients (n=16,818)	Missing %
Male (%)	77.5	0.0
Age (median, IQR)	68 (60-76)	0.2
Diabetes (%)	23.9	1.0
Hypertension (%)	61.9	2.5
Hyperlipidemia (%)	62.7	2.9
Smoking status (%)		6.2
Current smoker	19.9	
Previous smoker	40.2	
Previous MI (%)	37.2	3.8
Previous PCI (%)	18.4	0.1
Cardiogenic shock (%)*	10.2	1.2
Creatinine Clearance (ml/min)	81 (61-104)	28.2
CCS class (%)**		7.0
I	9.0	
II	52.2	
III	37.4	
IV	1.4	
Indication (%)		0.0
Stable CAD	45.5	
Unstable CAD/NSTEMI	27.5	
STEMI	14.3	
Other	12.7	
Extent of CAD (%)		1.1
1 vessel	20.4	
2 vessel	35.1	
3 vessel	36.1	
Left main disease***	8.4	

CAD: coronary artery disease, CCS: Canadian cardiovascular society, CTO: chronic total occlusion, IQR: inter quartile range, MI: myocardial infarction, (N)STEMI: (non-)ST-elevation myocardial infarction, PCI: percutaneous coronary intervention.

* Cardiogenic shock only displayed for the indication STEMI.

**CCS class only displayed for the indication stable CAD.

*** Left main (LM) disease includes: LM + 1 vessel, LM + 2 vessel and LM + 3 vessel.

Table 2. Baseline characteristics of patients from coronary segment subcohort with coronary artery disease, stratified for the presence of a CTO observed on angiography.

	CTO observed (n=14,609)	Missing %	CTO not observed (n=76,545)	Missing %	P-value
Male gender (%)	77.7	0	70.6	0.0	<0.01
Age (median, IQR)	68 (61-76)	0.2	68 (60-75)	0.2	<0.01
Diabetes (%)	24.0	1.0	18.6	0.8	<0.01
Hypertension (%)	62.0	2.4	52.5	2.0	<0.01
Hyperlipidemia (%)	61.9	2.8	44.4	2.5	<0.01
Smoking status (%)		5.8		5.5	<0.01
Current smoker	20.0		21.6		
Previous smoker	40.0		35.0		
Previous MI (%)	37.0	3.8	16.5	2.3	<0.01
Previous PCI (%)	17.5	0.1	10.7	0.05	<0.01
Cardiogenic shock(%)*	10.1	1.0	3.5	1.3	<0.01
Creatinine Clearance	80	28.2	81	34.2	<0.01
(ml/min)	(60-103)		(62-103)		
CCS class (%)**		6.9		5.5	0.19
I	9.3		9.6		
II	53.4		54.7		
III	36.0		34.5		
IV	1.3		1.2		
Indication (%)		0		0	<0.01
Stable CAD	44.5		17.1		
Unstable CAD/NSTEMI	26.3		49.6		
STEMI	15.1		26.0		
Other	14.0		7.3		
Extent of CAD (%)		1.5		1.2	<0.01
1 vessel	17.4		48.7		
2 vessel	35.1		25.9		
3 vessel	38.3		17.2		
Left main disease***	9.2		8.2		

CAD: coronary artery disease, CCS: Canadian cardiovascular society, CTO: chronic total occlusion, IQR: inter quartile range, MI: myocardial infarction, (N)STEMI: (non-)ST-elevation myocardial infarction, PCI: percutaneous coronary intervention.

* Cardiogenic shock only displayed for the indication STEMI

**CCS class only displayed for the indication stable CAD

*** Left main (LM) disease includes: LM + 1 vessel, LM + 2 vessel and LM + 3 vessel

stable CAD, a substantial proportion was diagnosed in patients with ACS. Furthermore, patients with a CTO more often presented in cardiogenic shock at presentation for STEMI compared to patients without a CTO. The CTO was more frequently located in the right coronary artery (RCA) followed by the left anterior descending artery (LAD) and left circumflex artery (LCx) (Figure 3). In approximately 14%, CTOs were observed in more than one vessel of which only 0.1% included the left main.

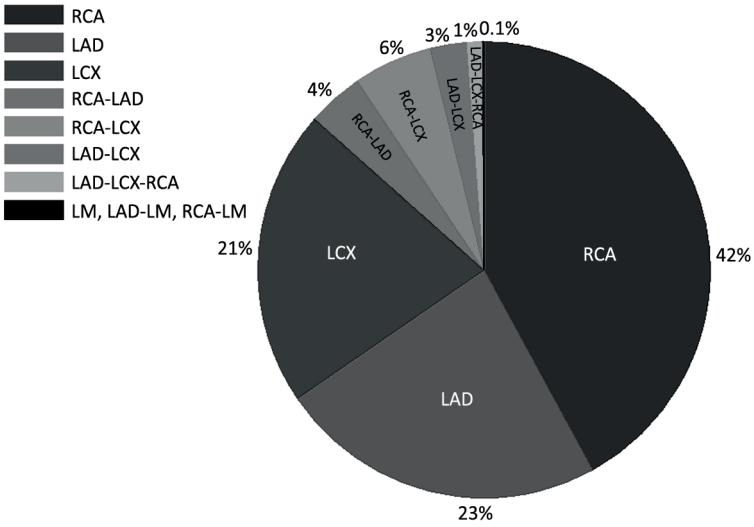

Figure 3. Coronary location of CTO observed at angiography.
RCA = right coronary artery, LAD= left descending coronary artery, LCx = left circumflex coronary artery, LM = left main.

Treatment of CTO patients

Table 3 shows the differences in baseline demographic and angiographic characteristics of CTO patients identified through the coronary segment stenosis, according to the received treatment at baseline. After diagnosis, the majority of the CTO patients (56%) received medical treatment only. The CTO patients who received invasive treatment were evenly distributed between PCI (22.3%) and referral for CABG (21.7%). CTO patients, who received medical treatment only, had more often previous MI, presented more often with STEMI, had a lower creatinine clearence and had less severe angina symptoms in comparison to the patients who were treated invasively for a CTO. Patients who were referred for CABG were more often male with a higher prevalence of cardiovascular risk factors including diabetes, had less often previous MI or PCI, presented more often with stable angina and suffered more frequently from extensive coronary artery disease than CTO patients treated with PCI. CTO patients treated for stable angina received medical

Table 3. Baseline characteristics of CTO patients from coronary segment subcohort according to the treatment strategy.

	No PCI of CTO		PCI of CTO		Referral for CABG		
	(n=8,182) (%)	Missing (%)	(n=3,251) (%)	Missing (%)	(n=3,172) (%)	Missing (%)	P-value
Male gender	76.2	0	76.5	0	82.9	0	<0.01
Age (median, IQR)	69 (61-77)	0.2	66 (59-74)	0.2	68 (61-74)	0.2	<0.01
Diabetes	24.0	1.1	21.0	1.2	26.9	0.4	<0.01
Hypertension	61.6	3.0	59.8	2.3	65.2	1.5	<0.01
Hyperlipidemia	58.6	3.4	60.2	2.7	71.2	1.3	<0.01
Smoking status		7.0		5.0		3.6	<0.01
Current smoker	21.4		20.7		15.5		
Previous smoker	39.4		39.5		42.1		
Previous MI	41.3	4.1	33.4	3.5	29.4	3.2	<0.01
Previous PCI	19.9	0.1	20.3	0.2	8.3	0.03	<0.01
Cardiogenic Shock*	10.0	1.0	10.4	0.9	0	0	0.84
Creatinine Clearance (ml/min) (ml/min	77 (57-101)	31.6	85 (65-109)	26.1	82 (64-102)	21.8	<0.01
CCS class**		7.1		4.6		7.8	<0.01
I	13.2		8.6		5.3		
II	55.2		56.3		49.8		
III	30.3		34.3		43.3		
IV	1.4		0.8		1.6		
Indication		0		0		0	<0.01
Stable CAD	33.1		41.3		77.4		
Unstable CAD/NSTEMI	31.1		39.8		0.4		
STEMI	21.7		13.5		0		
Other	14.2		5.5		22.2		

Table 3. Baseline characteristics of CTO patients from coronary segment subcohort according to the treatment strategy. (continued)

	No PCI of CTO		PCI of CTO		Referral for CABG		
	(n=8,182) (%)	Missing (%)	(n=3,251) (%)	Missing (%)	(n=3,172) (%)	Missing (%)	P-value
Extent of CAD (%)		1.2		1.3		1.3	<0.01
1 vessel	14.9		36.5		4.2		
2 vessel	40.9		39.6		15.8		
3 vessel	37.9		21.1		56.8		
Left main disease***	6.3		2.8		23.2		

CAD: coronary artery disease, CCS: Canadian cardiovascular society, CTO: chronic total occlusion, IQR: inter quartile range, MI: myocardial infarction, (N)STEMI: (non-) ST-elevation myocardial infarction, PCI: percutaneous coronary intervention.

* Cardiogenic shock only displayed for the indication STEMI.

**CCS class only displayed for the indication stable CAD.

*** Left main (LM) disease includes: LM + 1 vessel, LM + 2 vessel and LM + 3 vessel.

Data about initial treatment strategy were missing in four CTO patients.

treatment in 41.6%, PCI in 20.6% and CABG in 37.8%. CTO patients who were treated for acute coronary syndrome received medical treatment in 28.6%, PCI in 71.2%, and were referred to CABG in 0.2%. Procedure-related complications were reported in 5.4% CTO patients treated with PCI. The following complications were reported: death (0%), major bleeding (1.3%), stroke (0.3%), pericardial tamponade (0.4%) renal insufficiency (0.7%), emergency PCI (0.1%), emergency CABG (0%), procedure-related MI (1.1%), anaphylactic reaction (0.1%), other (1.4%)

Validation of CTO

The validation analysis revealed 36 (3.8%) erroneously classified patients. Of these, 18 patients did not have a 100% occluded coronary artery on the coronary angiogram. Another 5 patients had prior CABG and 13 patients had acute or subacute coronary occlusions.

DISCUSSION

In this study, we identified and studied 16,818 CTO patients in SCAAR. We found CTO in every tenth patient undergoing coronary angiography, and that the prevalence of CTO in Sweden decreased by one quarter in these patients between January 2005 and January 2012. The true prevalence of a CTO in the general population is unknown and not well studied. A few older studies based on small populations have reported the prevalence of CTO to be as high as 35%[7] and 52%[5] among patients with significant CAD. A recently published study[6] from Canada identified at total of 1697 CTO patients and reported its prevalence to be 14.7% in all patients who underwent coronary angiography. However, our study shows that the prevalence of CTO was 11.5% in SCAAR. The reason for the discrepancy in the prevalence of CTO between Swedish data and other countries may be explained by selection bias. While all previous studies derived their data from selected and relatively small populations, SCAAR contains data from all hospitals that perform coronary angiography and PCI in Sweden and thus selection bias is reduced. Another explanation may be that prevalence of CTO differs between the countries due to variance in severity of coronary artery disease, treatment algorithms for acute coronary syndromes and organization of health care system[11].

Our study shows that CTO patients are a high-risk population with more traditional cardiovascular risk factors, multivessel disease, history of MI and PCI, which is in accordance with previous reports[2,6,10]. Furthermore, a substantial number (14%) of patients had multiple CTO´s in separate vessels.

Majority of CTO patients had stable angina but approximately 40% had acute coronary syndrome at the time when CTO was diagnosed. Overall, 56% of the CTO patients were

treated with medical treatment initially. The remaining patients were evenly distributed between percutaneous and surgical revascularization similar to the Canadian study[9]. The success rate for CTO procedures in all Swedish hospitals was 53% which is lower than 70% and 80% reported by others[1,6,12]. However, the success rate in this study is based on all CTO procedures performed in our country rather than in a single hospital or smaller registries in other studies. The average success of 53% in SCAAR is unlikely to be representative for low- versus high-volume CTO centers[2,9]. Among the 30 hospitals reporting to SCAAR there are only a few high-volume centers with a dedicated CTO program and less than half of the CTO procedures in Sweden were performed at university hospitals. There is some evidence to suggest that procedural success is closely related to operator experience[13]. However, the recommendation that CTO procedures should be concentrated to dedicated high-volume hospitals needs stronger evidence.

Although CTO patients are common in clinical work, the evidence for the current guidelines and clinical practice is limited. The need for randomized clinical trials in this patient population is pressing; however, only a few such trials are initiated and ongoing[12,14]. Until evidence from RCTs becomes available we will need to identify and utilize the information available from contemporary databases and quality registries. The SCAAR registry with its distinctive structure covering the whole Swedish nation provides unique possibility to study several important features of CTO's including epidemiology, patients characteristic as well as health outcomes. It contains information about both past and current treatment strategies of these complex patients not only from specialized centers, but also from all hospitals that preforms PCI. Given these circumstances, the SCAAR registry can be an important instrument to address many key questions in CTO.

The prevalence of CTO in Sweden decreased by one quarter during the study period. We hypothesize that this primarily reflects the increasing rate of timely revascularisation with PCI of patients with acute coronary syndrome – STEMI and non-STEMI. Because the prevalence decreased by 25% while the number of procedures remained unchanged, the proportion of CTO procedures increased by the same percentage. Besides the decreased prevalence, the relatively low annual rate of CTO procedures in Sweden may be related to improved treatment of symptoms, better quality of life, fear of complications, technical complexity, and low evidence-level. There are some important limitations that need to be addressed. First, this is an observational study and as such it provides only associative evidence, not causative. Second, we cannot rule out the possibility of selection bias, as only hospitalized patients are included in the registry. Substantial proportion of missing data in the coronary segment subcohort may have resulted in biased estimate on CTO prevalence. Third, patients with missing data tend to have higher risk and their exclusion from the analysis might have produced biased results. Fourth, we cannot exclude the possibility that some occlusions had duration of less than three months,

however the validation of CTO diagnosis and procedures in SCAAR have shown that only 3.8% were erroneously classified.

CONCLUSION

SCAAR is the largest database of CTO patients to date. CTO is a frequent finding in Swedish population and is diagnosed in every 10th patient undergoing coronary angiography. The prevalence of CTO has decreased by one quarter. Patients with a CTO represent a high risk subgroup of CAD patients. SCAAR may be a valuable source of data in the process of evidence-building in the CTO field.

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Chapter 4

Prognostic Impact of Chronic Total Occlusions – A Report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

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JACC Cardiovascular Interventions, accepted

ABSTRACT

Objectives

Chronic total occlusions (CTO) are present in many patients with coronary artery disease and are difficult to treat with percutaneous coronary intervention (PCI). Our aim was to determine the prognostic impact of CTO on long-term mortality in a large prospective cohort.

Methods

The study population consisted of all consecutive patients who underwent coronary angiography in Sweden between January 1, 2005, and January 1, 2012 who were registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). The patient population was heterogeneous in regard to indication for angiography (stable angina, ST-elevation myocardial infarction (STEMI), unstable angina/non-STEMI, and other) and treatment options. We compared the long-term mortality rates of patients with and without CTO by using shared frailty Cox proportional-hazard regression adjusted for confounders. We tested for interactions between CTO and several prespecified characteristics: indication for angiography and PCI (stable angina, STEMI, unstable angina/non-STEMI, and other), severity of CAD (one-, two-, and three-vessel and/or left main disease), age, gender, and diabetes.

Results

During the study period, 14,441 CTO and 75,431 non-CTO patients were registered in SCAAR. CTO was associated with higher mortality (hazard ratio 1.29, 95% confidence interval 1.22–1.37, $P<0.001$). In subgroup analyses, the risk attributable to CTO was lowest in patients with stable angina and highest in those with STEMI. In addition, CTO was associated with highest risk in patients under 60 years of age and with lowest risk in octogenarians. There was no interaction between CTO and either diabetes or gender, suggesting an equally adverse effect in both groups.

Conclusions

In this large prospective observational study of patients with coronary artery disease, CTO was associated with increased mortality. This association was most prominent in younger patients and in patients with acute coronary syndromes.

INTRODUCTION

Chronic total occlusions (CTO) are present in ~16% of patients with significant coronary artery disease.(1) These lesions are difficult to treat with percutaneous coronary intervention (PCI) and are regarded as the remaining challenge in myocardial revascularization. PCI in patients with CTOs has gained much attention in recent years due to introduction of new techniques and devices resulting in high rate of procedural success. However, the scientific evidence for this treatment is based on retrospective studies and on expert consensus. Clear recommendation regarding the management of CTO patients are not available in European and in American guidelines.(2,3) No study has investigated the prognostic impact of CTO in patients with stable angina. In studies of the effects of CTO on short- and long-term mortality, CTO was associated with increased mortality(4) in patients with ST-segment elevation myocardial infarction (STEMI). However, these reports were based on subgroup analyses of observational databases and small cohorts. Therefore, larger studies are needed to establish the true effect of CTO on mortality in patients with coronary artery disease.

We identified a large prospective cohort of CTO patients registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)—a prospective national registry that accumulates data on all patients undergoing coronary angiography and PCI in Sweden.(1) The CTO cohort in SCAAR consists of more than 14,000 individuals with stable angina and acute coronary syndrome (ACS).

In this study, we analyzed data from the CTO cohort in SCAAR to determine whether CTO is associated with increased mortality in patients undergoing coronary angiography and/or PCI.

METHODS

Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

Established in 1999 as part of the national SWEDEHEART registry,(5) SCAAR gathers data on all consecutive patients from all hospitals that perform coronary angiography and PCI in Sweden. It is sponsored solely by the Swedish Health Authorities and receives no commercial funding. The registry's technology was developed and is administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has used a web-based case-report platform with automatic data surveillance. In total, 30 hospitals in Sweden, including nine university hospitals, have cardiac catheterization facilities. In SCAAR, a coronary angiography procedure is described by ~50 variables, and a PCI procedure by ~200 variables. After reviewing the clinical information, the PCI physician immediately enters clinical characteristics and procedural details into the registry. SCAAR obtains

data on patients' vital status continuously from the national death registry. Because use of personal identification numbers is mandatory, the death registry in Sweden has a high degree of completeness, but is not reviewed or adjudicated to establish cardiac vs. noncardiac causes of death.

Definitions

CTO was defined as 100% luminal diameter stenosis and absence of antegrade flow of at least 3 months duration (known or assumed).(6) The validity of this definition in SCAAR has been confirmed previously. (1) Coronary artery disease (CAD) was defined as a luminal narrowing ≥50% on angiography. PCI was considered successful if the residual stenosis was <50%, the stenosis grade decreased by at least 20%, TIMI flow was III, and there were no serious complications during hospitalization. Proximal CTOs were defined those in segments 1–3 [right coronary artery (RCA)], 5 (left main), 6 and 7 [(left anterior descending artery (LAD)], and 11 and 12 [left circumflex artery (LCx)]. CTOs in all other segments were defined as distal.

Study Cohort

The study is based on patients who underwent diagnostic coronary angiography and were registered in SCAAR between January 1, 2005, to January 1, 2012 (Figure 1). Only patients diagnosed with significant CAD were included in the analyses. A CTO patient was identified from available information about the percentage of luminal stenosis at the level of the coronary segments. Information from a diagnostic coronary angiogram could also be used to determine whether a coronary segment was totally occluded. To differentiate between acute and chronic occlusions, we excluded patients who underwent a procedure for ACS in whom the 100% occlusion was located in the same coronary artery as the culprit vessel. Patients who had a procedure in the same vessel within the previous 3 months were also excluded. Patients who had undergone previous coronary artery bypass graft (CABG) surgery were excluded from analysis, as graft patency could not be determined. The study was approved by the regional ethical board in Gothenburg according to Swedish law and regulations.

Statistical Analysis

To compare the clinical characteristics of the groups, we used the chi-square test for categorical variables and the Mann-Whitney U and Kruskal-Wallis tests for continuous non-normally distributed variables. The Shapiro-Wilks test was used to assess normal distribution. $P<0.05$ was considered statistically significant. The primary outcome was all-cause mortality. Unadjusted survival was examined with Kaplan-Meier survival curves and the log-rank test. To evaluate the association between CTO and mortality, we used Cox proportional-hazards regression models to calculate multivariable-adjusted

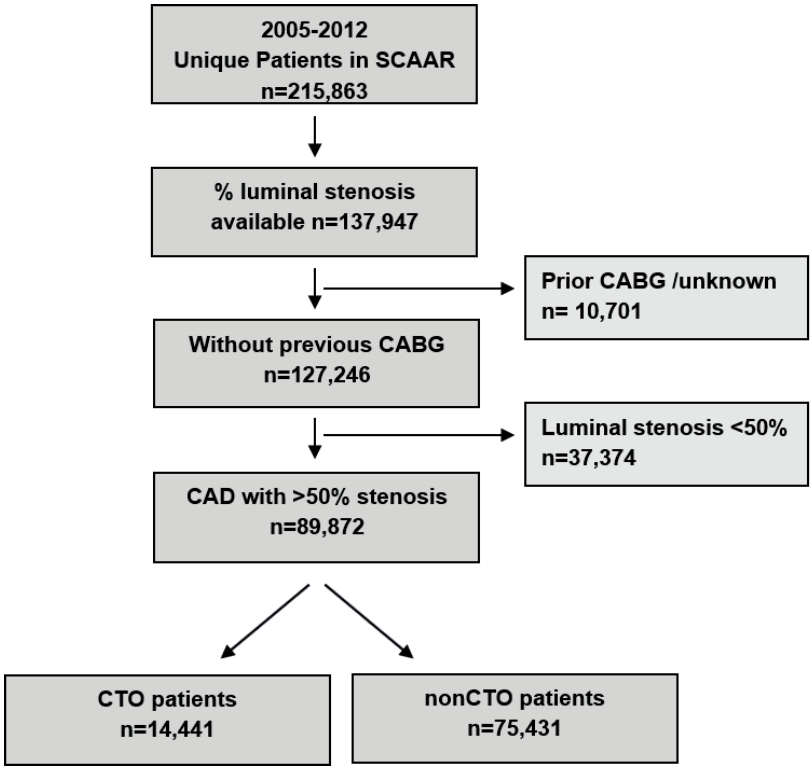

Figure 1. Flow chart for patient inclusion.

hazard ratios (HRs). Because SCAAR has a hierarchical structure and patients are clustered by hospital, the assumption of independence between patients was violated. To adjust for this clustering effect, we used multilevel modeling and shared frailty Cox proportional-hazards regression(7) as the primary model. We scrutinized the database for missing data and found that a number of variables had missing data. Thus, in addition to the complete case analysis, we used the multiple imputation method to estimate the missing data(8,9). We performed shared frailty Cox proportional-hazards regression of the imputed data set under the assumption that the data were missing at random. For the imputation protocol, we analyzed 20 imputed data sets with the chain-equation method(10) and a predictive-mean matching algorithm, which used the same covariates as the main analysis plus a cumulative hazard and event indicator. The secondary model was complete-case analysis based on shared frailty Cox proportional-hazards regression which included only cases with available data for all variables listed in Table 1. The results from secondary models are presented in the supplement. All tests were two-sided.

Table 1. Baseline Characteristics of Patients with and without CTO.

Characteristic	CTO n=14,441	Missing n (%)	Non-CTO n=75,431	Missing n (%)	P
Male, %	77.7	0	70.7	0	<0.01
Median age, y (IQR)	68 (61–76)	289 (0.02%)	68 (60–75)	150 (0.2%)	<0.01
Age (%)					<0.01
0-59	21.7		24.3		
60-79	63.7		62.1		
≥80	14.6		13.6		
Diabetes, %	23.7	144 (1%)	18.4	603 (0.8%)	<0.01
Hypertension, %	60.4	361 (2.5%)	51.4	1,509 (2%)	<0.01
Hyperlipidemia, %	60.2	404 (2.8%)	43.3	1,886 (2.5%)	<0.01
Smoking status, %		838 (5.8%)		4,149 (5.8%)	<0.01
Current smoker	18.8		20.5		
Previous smoker	37.6		33.1		
Previous MI, %	35.5	549 (3.8%)	16.1	1,735 (2.3%)	<0.01
Previous PCI, %	17.4	12 (0.08%)	10.6	38 (0.05%)	<0.01
Indication, %		0		0	<0.01
Stable CAD	44.6		17.1		
Unstable CAD*	26.4		49.7		
STEMI	15.1		26.0		
Other	14.0		7.2		
Extent of CAD, %		3 (0.02%)		53 (0.07%)	<0.01
One vessel	17.4		48.6		
Two vessel	35.1		26.0		
Three vessel	38.3		17.2		
Left main†	9.2		8.2		
Puncture site, %		4 (0.03%)		15 (0.02%)	<0.01
Femoral	46.7		48.8		
Radial	53.3		51.2		
Any complication, %	3.9	0	4.2	8 (0.01%)	0.14
Primary decision, %		4 (0.03%)		8 (0.01%)	<0.01
Conservative	15.9		12.0		
PCI	62.3		72.3		
CABG surgery	21.9		15.9		
CTO vessel, %		0		0	
RCA	42.1		NA		
LAD	23.4		NA		
LCx	21.1		NA		
Multiple vessels	13.5		NA		
CTO location		0		0	
Proximal	64.2				
Distal	35.8				

IQR: interquartile range.

*Unstable CAD includes unstable angina and non-ST-elevation myocardial infarction.

†Includes left main plus one-, two-, or three-vessel disease.

Potential confounders (Table 1) were all entered into the model. Six subgroup analyses were prespecified for the following patient categories: indication for angiography and PCI (stable angina, UA/non-STEMI, STEMI, and other), severity of CAD (one-, two-, and three-vessel and/or left main disease), age, gender, diabetes, and calendar year. The possible effect modification of CTO on risk of dying in the subgroups was analyzed by interaction test. To assess its interaction with CTO, age was examined as both a continuous variable and a factorial variable consisting of four age groups (<59, 60–69, 70–79, and >80 years). Localization of CTO (i.e. LAD, LCx, RCA and multiple CTOs) and presence of CTOs in proximal vs. distal coronary segments were evaluated by entering these variables separately into the regression. The assumption of proportional hazards for each covariate was reviewed separately by log-minus-log survival plots and by a formal test based on scaled Schoenfeld residuals. Possible multi-colinearity between the variables in the model was assessed by calculating the variance inflation factor.

Cumulative hazard was estimated with Nelson-Aalen's test. All analyses were performed with Stata software (version 13.1, StataCorp, College Station, TX). Rubin's protocol(11) was used for the imputation procedure and subsequent Cox proportional-hazards regression estimation.

RESULTS

Patients and Procedures

The details about patient's selection are presented in Figure 1. We identified 14,441 CTO patients and 75,431 non-CTO patients. Patient's characteristics are described in Table 1 and in the supplement.

CTO and Long-Term Mortality

The mean follow-up time was 3.2 years for the CTO group and 3.1 years for the non-CTO group. No patients included in the study were lost to follow-up. The mortality rate was higher in CTO patients (unadjusted HR 1.41, 95% confidence interval (CI) 1.35–1.48, *P*<0.001, Figure 2). After adjustment, CTO remained an independent predictor of long-term mortality (primary model: HR 1.29, 95% CI 1.22–1.37, *P*<0.001; complete case analysis: HR 1.27, 95% CI 1.20–1.35, *P*<0.001) (Table 2 and Figure 2). The risk (per-unit-time) decreased rapidly in both groups during the first 12 months after angiography; it was lowest between 2 and 3 years after the index procedure but remained constant and substantially higher in the CTO group until the third year (Figure 3). In the non-CTO group, the risk gradually increased from the end of the second year to the fifth year. The interaction between CTO and calendar year was significant (*P*<0.001). As shown by trend tests, risk in the non-CTO group gradually decreased throughout the study period. In

Table 2. Multivariable Cox Proportional-Hazards Regression Analysis.

Characteristic	HR	95% CI	P
CTO	1.29	1.22–1.37	<0.001
Age, y	1.08	1.07–1.08	<0.001
Male	0.99	0.95–1.04	0.733
Smoking			
Never	Reference		
Previous	1.19	1.13–1.25	<0.001
Current	1.83	1.72–1.94	<0.001
Hypertension	1.07	1.02–1.11	0.003
Hyperlipidemia	0.91	0.87–0.96	<0.001
Diabetes mellitus	1.69	1.62–1.77	<0.001
Previous MI	1.49	1.42–1.57	<0.001
Previous PCI	0.94	0.89–1.01	0.078
Indication			
Stable angina	Reference		
Other	2.65	2.43–2.83	<0.001
Unstable angina/non-STEMI	1.65	1.55–1.76	<0.001
STEMI	2.34	2.17–2.52	<0.001
Severity of CAD			
One-vessel	Reference		
Two-vessel	1.16	1.10–1.22	<0.001
Three-vessel	1.45	1.37–1.53	<0.001
Left main	1.86	1.73–1.99	<0.001
Hospital volume			
Low	Reference		
Middle	1.07	0.95–1.20	0.261
High	1.08	0.95–1.22	0.245
Year of procedure (2005–2012)	0.98	0.97-0.99	0.023†
CTO*year‡	1.06	1.03-1.08	<0.001
Puncture site			
Femoral	1.27	1.21–1.34	<0.001
Any complication	1.45	1.33–1.58	<0.001
Primary decision§			
No intervention	Reference		
PCI	0.63	0.59–0.67	<0.001
CABG	0.64	0.60–0.66	<0.001

IQR: interquartile range.

†Test for trend.

‡Interaction term between "year of procedure" and CTO.

§The variable represents the operators' decision, after diagnostic angiography, to treat all lesions. This decision is not specific for treatment of CTOs.

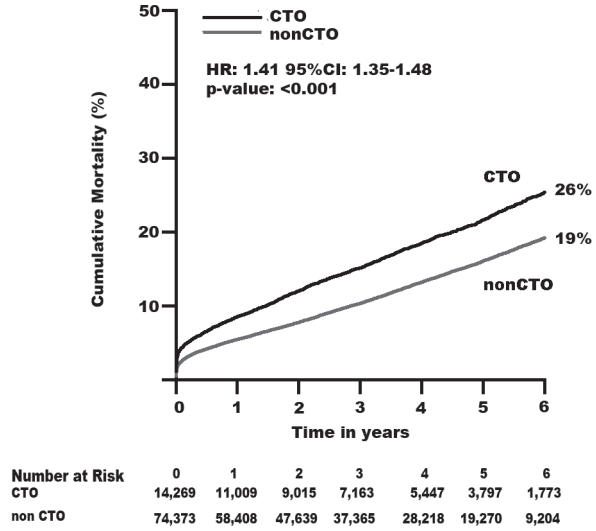

Figure 2. Crude Kaplan-Meier curves for long-term mortality in patients with and without CTO in SCAAR.

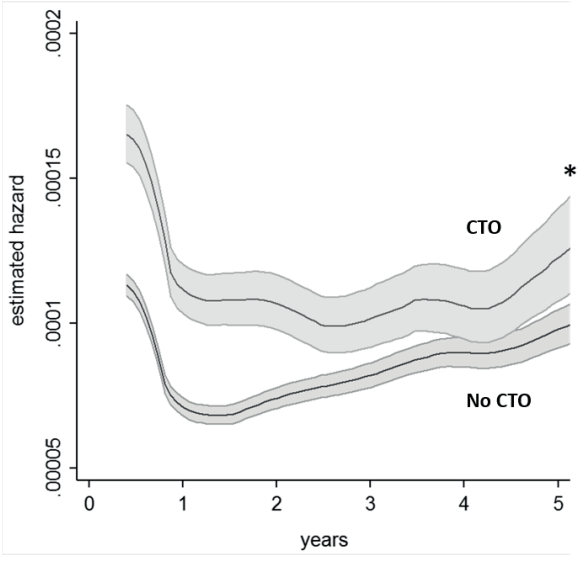

Figure 3. Estimated hazard with 95% confidence interval as a function of time.
*The curve is truncated at 5.5 years of follow-up.

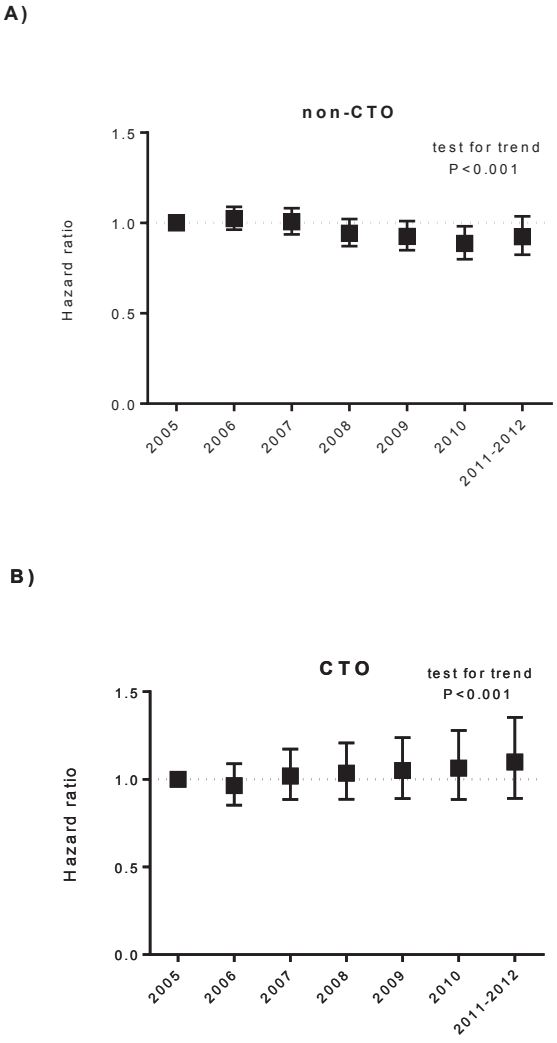

Figure 4. Hazard ratio in the CTO (A) and non-CTO (B) groups between 2005 and 2012. The reference year was 2005. Relative risk decreased steadily in the non-CTO group but increased gradually in the CTO group.

contrast, risk in the CTO group increased on average by 6.6% each year (HR 1.06, 95% CI 1.06–1.07, *P*<0.001) (Figure 4). CTO patients with history of previous MI had higher mortality risk than CTO patients without previous MI (HR 1.39, 95% CI 1.28 – 1.52, P < 0.001).

Successful Versus Unsuccessful Revascularization of CTO and Mortality

During the study period 6442 patients underwent PCI for CTO. Successful revascularization of CTOs was achieved in 54.2% of cases and was associated with lower risk of death compared to unsuccessful PCI of CTO (HR 0.85 95% CI 0.73-0.98, P<0.034) (Figure 7).

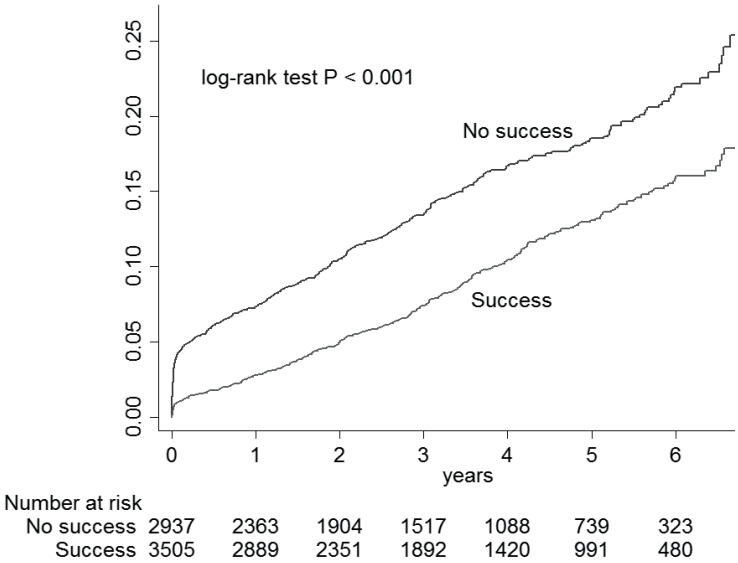

Figure 7. Crude Kaplan-Meier curves for long-term mortality in CTO patients after successful versus failed PCI.

CTO in Patient Subgroups

Indication

The indications for coronary angiography in SCAAR during the study period were categorized as stable angina, unstable angina (UA)/NSTEMI), STEMI, and other. The last group consisted of patients who underwent angiography before valve surgery or for unexplained chest pain, heart failure/cardiomyopathy, pre-transplantation diagnosis and post-transplantation follow-up, arrhythmias, aortic aneurysm/dissection, and cardiac arrest. There was a significant interaction between the presence of a CTO and indication (*P*<0.001). As shown by Forest plot, risk increased gradually as the indication for angiography shifted from stable angina to ACS, culminating with the highest risk in STEMI patients (Figure 5). The primary model with imputation of missing data and complete case analysis showed similar point estimates for HR (other: HR 1.19, 95% CI

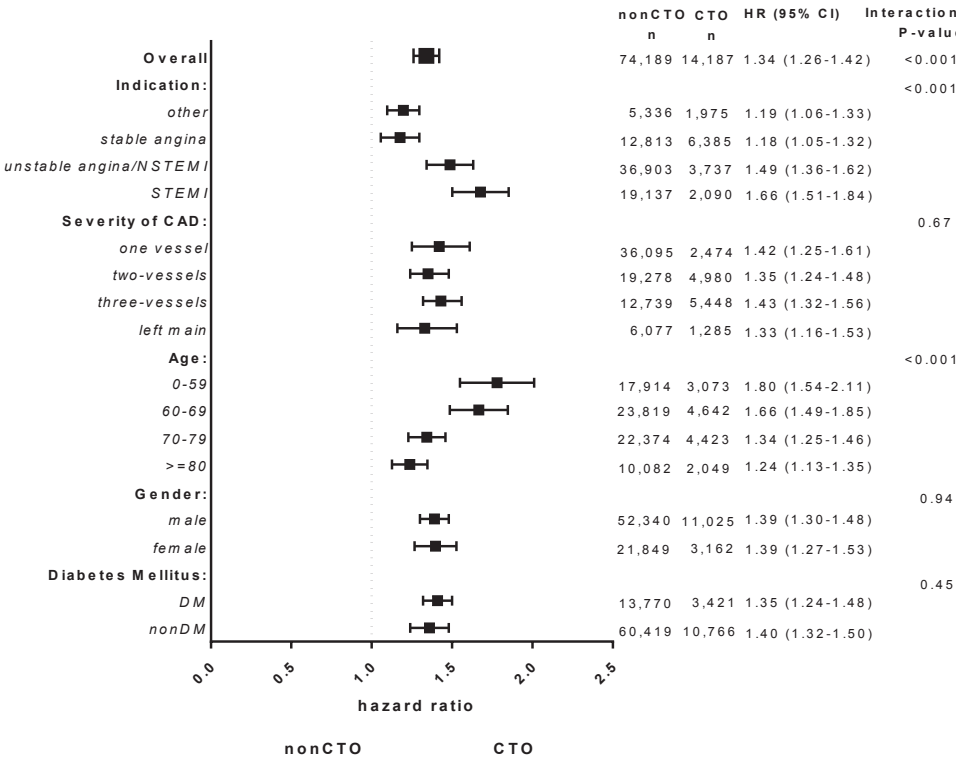

Figure 5. Forest plot showing interactions between CTO and different patient characteristics.

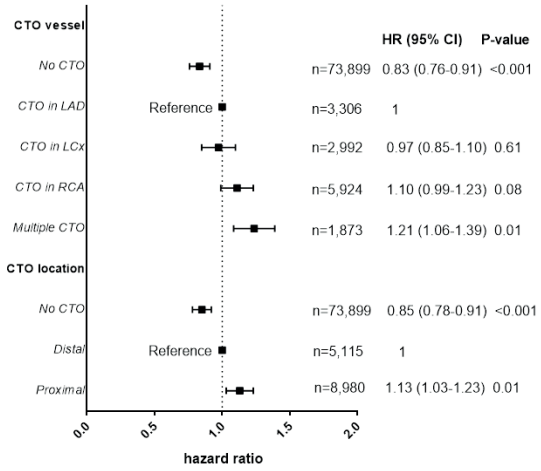

Figure 6. Forest plot showing HR for CTO in different coronary arteries and for proximal and distal location of CTO.

1.06–1.33, *P*=0.003; stable angina: HR 1.18, 95% CI 1.05–1.32, *P*=0.005; UA/NSTEMI: HR 1.49 95% CI 1.36–1.62, *P*<0.001; STEMI: HR 1.66, 95% CI 1.51–1.84, *P*<0.001).

Severity of CAD

The majority (83%) of patients had multivessel disease. Multivessel disease was associated with a higher mortality risk than one-vessel disease (*P*<0.001, Table 2). We found no interaction between CTO and the severity of CAD (Figure 5).

CTO localization

Patients with multiple CTOs had highest risk of dying (Figure 6). We found no difference between CTOs in the LAD and those in the LCx (HR 0.97, 95% CI 0.85–1.10, *P*=0.61) or RCA (HR 1.10, 95% CI 0.99–1.23, *P*=0.08). CTOs in proximal segments were associated with a higher risk than CTOs in distal segments (HR 1.13, 95% CI 1.03-1.23, *P*=0.01). Patients with CTO in distal segments had higher mortality risk than patients without CTO.

Age

One fifth (21.7%) of all CTO patients were younger than 59 years of age, and 14.6% were octogenarians. When age was entered in the Cox proportional-hazards regression as a continuous variable in interaction with CTO, the HR decreased by ~2% per year of age (HR 0.98, 95% CI 0.98–0.99, *P*<0.001). The interaction between CTO and the four different age categories is shown in Figure 5. HR was highest in CTO patients below 59 years and was lowest in octogenarians.

Gender

The majority of patients in the study were men (Table 1). However, there were more than 20,000 women, of whom at least 3,000 had a CTO. CTO was associated with an equally negative prognosis in men and women. The interaction between CTO and gender was not significant in the primary model (Figure 5).

Diabetes mellitus

Diabetes was present in approximately one fifth of all patients. Women with CTO were more likely to have diabetes (28% vs. 22%, *P*<0.001). CTO did not interact with diabetes, suggesting that a CTO has a similarly adverse prognosis in patients with and without diabetes (Figure 5).

DISCUSSION

We investigated the effect of CTO on mortality in 14,441 CTO patients in the prospective SCAAR database. We found that CTO is associated with moderately increased risk of long-term mortality. While mortality decreased between 2005 and 2012 in patients without CTO, it increased on average by 6.6% annually in patients with CTO. In CTO patients, the mortality was highest in younger patients and in those with ACS.

The large number of prospectively followed CTO patients in SCAAR provided a unique opportunity to evaluate the association between CTO and survival rate both in the whole SCAAR cohort and in several important subgroups. The divergence in the mortality trends of patients with and without CTO has not been previously reported. Since the mortality rate in CAD patients has fallen substantially over the last 20 years in Sweden,(12) this divergence was unexpected and puzzling. At the same time, it emphasizes the clinical importance of CTO. This unanticipated divergence in mortality could reflect an upsurge in the use of coronary angiography in patients with increasingly complex disease in whom CTO is frequently diagnosed. In Sweden, the use of PCI in patients with stable angina and ACS increased steadily from ~18,000 in 2005 to 21,000 in 2012, but the number of PCIs for CTO remained low (~1100/year) during the same period(1). It is also possible that modern pharmacological treatment is less effective in patients with CTO. These two factors could at least partly explain the divergent trends in mortality.

Another novel and important observation was the association of CTO with moderately increased mortality risk. Specifically, risk increased gradually, being lowest in patients with stable angina, somewhat higher in UA/NSTEMI, and highest in patients with STEMI. This risk gradient strengthens the case for a causal relationship between CTO and mortality. The mechanism for this observation is not established, but our finding is both biologically plausible and intuitively appealing. Most patients (>90%) with symptomatic CTO who have well-developed collateral circulation still have ischemia during exercise.(13) An increased ischemic burden due to a CTO, combined with ongoing ischemic cellular damage, could lead to greater contractile dysfunction, larger infarct size, and electrophysiological instability. The importance of a CTO in patients with MI and the effect of hemodynamic instability has been noted in smaller studies.(14) The most prominent effect of a CTO on mortality was in STEMI patients. This finding may reflect more pronounced and rapid development of pathologic postinfarction remodeling, leading to left ventricular dysfunction and heart failure, both of which predict increased risk for sudden death.(15,16)

There is unequivocal evidence that increasing age is associated with higher mortality in ischemic heart disease. Some studies suggest that men have a higher risk of dying after ACS, while others suggest that younger women may be at highest risk. In line with this reasoning, we modeled the possible interactions between CTO and age and CTO

and gender and found evidence for yet another risk gradient. In this analysis, CTO was associated with highest risk in younger patients, and the risk gradually decreased with advancing age. This novel finding may reflect the shorter life expectancy and the greater frequency of other strong risk factors in the elderly. The possible interaction between gender and CTO was not addressed previously. Our analysis, which included over 3,000 women with CTO, showed that CTO is associated with an equally negative prognosis in both men and women.

Another important observation was that CTO did not modify the adverse prognostic effect of severity of CAD. In other words, a patient with a CTO has higher risk of dying than a patient without CTO who has an equivalent degree of CAD. Previous reports proposed that CTO mainly explains the difference in mortality between patients with single-vessel and multivessel disease. Our findings do not support this view. Although CTO is often seen as the final stage of CAD, our study suggests that a CTO can be viewed as a distinct biological property of an individual, since both CAD severity and CTO were independent predictors of mortality in the absence of an effect modification of one variable on the other. Diabetes had an equally adverse prognostic impact in patients with and without CTO. By contrast, in earlier reports of STEMI patients, CTO was associated with a worse prognosis in patients with diabetes. The discrepancies between this study and previous reports may reflect differences in statistical modeling for subgroup analysis, statistical power, and selection bias.

We identified a large number of patients with CTOs in more than one vessel. These patients had a worse prognosis than those with CTOs in a single vessel. We found no significant difference in the risk between CTOs in different coronary vessels. However, within the same vessel, a CTO in proximal segments had worse prognosis than a CTO in distal segments. Even the CTO in distal segments was associated with the worse prognosis. The fact that both multiple CTOs and CTOs in both proximal and distal segments were associated with higher risk supports the hypothesis that the negative impact of CTO on survival is mediated by the severity and extent of the ischemic burden. This risk gradient strengthens the causative relationship between CTO and mortality.

Our study provides new and stronger evidence for a possible causal relationship between CTO and increased mortality. At the same time it poses the question of whether successful revascularization can reduce or eliminate the increase in risk of mortality. It is still a matter of debate whether revascularization in patients with stable angina improves survival. There is some evidence that revascularization is protective in patients with severe CAD, diabetes, and a large area of inducible ischemia.(17-21) In contrast, the evidence is much stronger that early revascularization reduces the frequency of adverse cardiovascular events in patients with ACS.(22-26) We hypothesize that the clinical benefit and cost-effectiveness are greater after successful revascularization of CTO patients, particularly in younger patients and in those with ACS. Currently, no data is available

from randomized clinical trials to support this hypothesis. In observational studies of patients with CTO, successful revascularization alleviated angina, increased electrical stability, reduced the need for CABG, improved left ventricular function, and increased survival.(15,16,27) Our study confirms the results from previous smaller observational studies that successful revascularization of CTO is associated with improved survival. However, the value of these studies, including our own data, for clinical decision-making is considerably limited, as they compared successful and failed intervention without including patients on optimal medical treatment as a control group. Furthermore, all observational studies were conducted in patients with stable angina who have lower risk for adverse cardiovascular events and for procedure-related complications than patients with ACS. The OAT trial did not demonstrate improvement in clinical outcomes after revascularization of infarct-related artery in stable STEMI patients with subacute occlusions.(28) Recently completed EXPLORE trial based on 304 CTO patients did not show benefit of routine revascularization of CTO in non-culprit coronary artery on LV function and morphology in subacute phase of STEMI.(29) Consequently, the totality of evidence from randomized clinical trials to date speaks against routine revascularization of stable ACS patients with CTO in non-culprit coronary arteries.

Currently, two randomized controlled trials of PCI in patients with CTO are ongoing: EUROCTO and DECISION-CTO. These trials will provide additional valuable information about whether PCI is superior to medical therapy in reducing symptoms and improving quality of life, exercise tolerance, left ventricular function and morphology, and safety. However, the trials are not designed to produce decisive evidence about how revascularization affects survival. Under these circumstances, the results from large observational studies such as ours may be useful for clinical decision-making and to support treatment recommendations.

Our study has several important limitations that need to be addressed. First, it was an observational study and as such it provides only associative evidence, not causative. We cannot rule out the possibility of selection bias, residual confounding and survival bias, as only surviving hospitalized patients are included in the registry. On the other hand, the observational nature of our study provides real-world data on the largest cohort studied to date. Second, information about angiographic findings at the segmental level was missing in 42.2% of patients and this could have introduced bias in risk estimates. Third, SCAAR does not contain data on pharmacological treatment, presence of ischemia or viability, patient frailty, and we were not able to adjust for the possible differences known to affect clinical outcome. Fourth, we did not have data on cause-specific mortality. Lastly, we did not have data about outcome of revascularization of CTOs with CABG.

In conclusion, we found that a CTO is associated with increased risk of mortality in patients with CAD, especially in younger patients and in those with ACS.

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SUPPLEMENTARY APPENDIX

Patients and Procedures

During the study period, 276,931 coronary angiographies and/or PCI procedures in 215,836 patients were performed in Sweden. Complete information about percent stenosis in coronary segments was available in 160,159 (57.8%) angiographies, of which 144,744 were in patients without previous CABG. In total, 89,872 patients without previous CABG had >50% luminal stenosis on angiography, and 14,441 had a CTO. There were 75,431 non-CTO patients. CTO patients were more often male and were more likely to have diabetes, hypertension, hyperlipidemia, previous MI, and previous PCI (Table 1). The extent of CAD was also more severe in CTO patients. CTO was diagnosed in the majority of cases during coronary angiography for stable CAD; however, 41.5% of CTOs were in patients with ACS. The CTO was located most often in the RCA (42%), followed by the LAD (23%) and the LCx (21%). In approximately 14% of patients, CTOs were present in more than one vessel. CTOs were more frequent in proximal segments (64.2%) than in distal segments (35.8%).

CTO and Long-Term Mortality

For sensitivity analysis of our primary model we used propensity score (PS) adjustment. We calculated generalized PS for each patient using logistic regression according to Hirano et al.[11] using dedicated Stata package[12]. For the PS stratification analyses, strata were created based on PS quintiles. Formation of five strata based on the PS values removes >90 % of the bias in each of the included covariates in the propensity model[13]. The following covariates were entered into the multivariable logistic regression regression: age, gender, body mass index, hypertension, diabetes mellitus, tobacco use, hyperlipidemia, previous myocardial infarction (MI), previous PCI, previous CABG, indication for coronary angiography, severity of coronary artery disease, hospital volume of coronary angiography and PCI, year of procedure, puncture site, complications and primary decision after diagnostic angiography (medical treatment, PCI, CABG). The calculated PS was entered into the Cox proportional-hazards regression as quintiles of PS. We assessed goodness-of-fit (calibration) for the models was using the Hosmer-Lemeshow test. The discriminative ability of the model was assessed using the c-statistic. Estimated mortality risk associated with the presence of CTO based on adjustment with PS (HR 1.34; 95% CI 1.28 - 1.41) was similar to the risk estimation based on the main model (HR 1.29; 95% CI 1.22 - 1.37).

CTO in Patient Subgroups

Severity of CAD

Complete case analysis showed similar results as the primary model. Multivessel disease was associated with increased mortality compared to one vessel disease (two-vessel: HR 1.14, 95% CI 1.08–1.20, *P*<0.001; three-vessel: HR 1.34, 95% CI 1.26–1.41, *P*<0.001; left main: HR 1.57, 95% CI 1.47–1.69, <0.001). There was no significant interaction between CTO and severity of CAD in complete case analysis.

Age

Complete case analysis showed similar results as the main model (HR 0.98, 95% CI 0.98–0.99, *P*<0.001) for every year of increased age in the presence of a CTO. Complete case analysis with age categorized into four groups showed similar results as the main model (age <59: HR 1.64, 95% CI 1.38–1.94, *P*<0.001; age 60–69: HR 1.48, 95% CI 1.32–1.65, *P*<0.001; age 70–79: HR 1.23, 95% CI 1.13–1.33, *P*<0.001; age >80: HR 1.13, 95% CI 1.03–1.25, *P*<0.001).

Gender

Complete case analysis showed similar results as the main model (men: HR 1.25, 95% CI 1.18–1.34, *P*<0.001; women: HR 1.21, 95% CI 1.09–1.34, *P*<0.001).

Diabetes

Complete case analysis showed similar results as the main model (diabetes: HR 1.26, 95% CI 1.16–1.38, no diabetes HR 1.30, 95% CI 1.22–1.38, *P*<0.001; *P*<0.001).

Part II

Chronic total coronary occlusion in stable coronary artery disease

Chapter 5

Long-Term Clinical Outcomes after Percutaneous Coronary Intervention for Chronic Total Occlusions in Elderly Patients (≥75 years): Five-Year Outcomes from a 1,791 Patient Multi-National Registry

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Catheterization and Cardiovascular Interventions 2013 Jul;82(1):85-92

ABSTRACT

Objective

To investigate procedural success rates and long-term clinical outcome of percutaneous coronary intervention (PCI) for chronic total occlusions (CTO) in elderly patients

Background

Little is known about procedural success and long-term clinical outcome of PCI for CTO in the elderly.

Methods

A total of 1791 consecutive patients with 1852 CTO underwent PCI at three large centers in USA, Italy and South Korea. Outcomes included procedural success and major adverse cardiac events (MACE, composite of mortality, myocardial infarction or coronary artery bypass graft surgery [CABG]). Time-to-event analyses were performed using Kaplan-Meier statistics and the log-rank statistic was used to test for differences between pts aged ≥75 and pts aged <75 years.

Results

213 patients (12%) were aged ≥75 years. Procedural success rates were similar in elderly patients compared with patients <75 years (63.8% vs. 69.1%, p=0.12). Median follow-up was 890 days (IQR 380-1480 days). MACE rates after successful vs. failed PCI were 25.8% vs. 42.3% in the elderly (p=0.02) and 11.2 vs. 20.8% in younger patients (p<0.01). In elderly patients, this reduction in MACE after successful PCI was mainly driven by a reduction in CABG (0.0% vs. 20.4%, p<0.01), there were no significant differences in terms of mortality (19.6% vs. 24.6%, p=0.13) or MI (11.5% vs 8.0%, p=0.87).

Conclusion

CTO PCI in patients ≥75 years has similar success as in patients <75 years. In elderly patients undergoing CTO PCI, MACE rates were relatively high but successful revascularization is associated with a reduction in MACE at 5-year follow-up in both elderly and younger patients.

INTRODUCTION

The proportion of elderly people in the general population has been increasing. [1] The limited representation and focus on elderly patients in medical literature has resulted in insufficient data about the effectiveness of various strategies in this population. Chronic total occlusions (CTO's) of coronary arteries are frequently (18-30%) encountered on diagnostic coronary angiograms and a recent publication showed that advancing age increases the likelihood to detect a CTO on diagnostic coronary angiography.[2,3] The presence or absence of a CTO appears to play a pivotal role in the treatment strategy. Several observational studies have shown that the majority of CTO patients receiving revascularization will be referred for coronary artery bypass (CABG) surgery.[2,4] Successful percutaneous coronary intervention (PCI) of CTO's is associated with symptom relief, a lower rate of subsequent myocardial infarction (MI), coronary artery bypass graft (CABG) surgery and improvement of long-term survival compared to unsuccessful PCI.[5-9] However, these procedures are one of the major challenges in current interventional cardiology with low success rates (60-85% rather than over 95% for typical PCI cases), longer procedural time, more contrast use and higher rate of complications.[10,11] As the elderly represents a large proportion of the daily clinical ''real world" practice, the need for more information is high as the anticipated benefits and possible risks of many treatments can differ with age. However, the absence of clinical data in the elderly population should not imply a non-performance of PCI due to perception of prohibitive complications or low success rate in this population. Therefore, the aim of the current study was to investigate the procedural success rates and long-term clinical outcome of successful versus failed CTO revascularization in patients ≥75 years.

METHODS

All patients who underwent PCI for at least one CTO at three tertiary care hospitals between 1998 and 2007 were included in this study. A CTO was defined as a coronary artery obstruction with a Thrombolysis in Myocardial Infarction (TIMI) flow grade 0. All patients included had a native vessel occlusion estimated to be of at least three-month duration based on either a history of sudden chest pain, a previous myocardial infarction in the same target vessel territory, or the time between diagnosis made on coronary angiography and PCI. All patients had symptomatic angina and/or a positive functional ischemia study.

PCI and stent implantation were performed in a standard manner. Heparin was administered to maintain an activated clotting time >250 seconds. The use of bare-metal stents (BMS) or DES as well as the use of glycoprotein IIb/IIIa inhibitors was left to the discretion

of the treating physician PCI of the CTO was performed using contemporary techniques such as bilateral injection, specialized hydrophilic, tapered tip, and stiff wires, parallel wires, microcatheters, and retrograde approach when they became available. After PCI, all patients were prescribed lifelong aspirin, in addition clopidogrel was prescribed for at least 3 months after DES implantation in Italy and South Korea, and for at least 12 months in the US, and at least 1 month after BMS implantation in all participating sites.

Demographic, angiographic, and procedural data regarding all patients undergoing PCI at the three participating centers (n=1,791) were prospectively entered into a dedicated database. Patients were followed prospectively by telephone interview or outpatient visit after 30 days, and yearly thereafter. Demographic, angiographic, procedural and follow-up data were subsequently merged in the multinational CTO registry, containing all data contributed by the three participating centers. The following endpoints were analyzed: all-cause mortality, myocardial infarction (MI) and need for CABG at 5-year follow-up. Additionally, we evaluated a composite endpoint of major cardiovascular events (MACE), consisting of all-cause mortality, MI, and CABG. Endpoint definitions have been previously published in detail.[10] Multivessel disease was defined as the presence of at least one stenosis ≥70% by visual assessment in another major epicardial vessel or its sidebranches than that where the CTO was located. Procedural success was defined as successful recanalization and dilatation of at least one CTO per patient with or without stent implantation, residual stenosis of <50% and TIMI flow ≥2.

Statistical analysis

For the purpose of the current analysis we defined patients aged ≥75 years as elderly. Data are presented as the mean ± standard deviation or as percentages. Event rates were estimated using the Kaplan-Meier method. Follow-up was censored at date of last follow-up or at 5 years, whichever came first. Survival curves using all available follow-up data were constructed for time-to-event variables using Kaplan-Meier methodology. Event rates were compared by log-rank test. We created a multivariate Cox regression model to identify

independent predictors of MACE in the complete study population and additionally separate models for elderly and young patients. In order not to over-fit the model we included only the following covariates: age (in years), diabetes mellitus, chronic kidney disease, and procedural success. A forward stepwise selection of variables was employed with $p<0.05$ as threshold for inclusion and $p>0.10$ as threshold for removal from the model. Additionally, we performed a formal interaction test to determine whether age ≥75 years affected the risk of MACE after successful versus failed PCI. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Il).

RESULTS

During the study period, 1,791 patients underwent PCI of at least one CTO. A total of 213 (11.9%) of patients were aged ≥75 years. Table 1 shows baseline demographic, angiographic and procedural characteristics of patients <75 years and patients ≥75 years. Elderly patients who received CTO revascularization had a mean age of 79±3.3 years and were predominantly male. Furthermore, there is a notable presence of the traditional cardiovascular risk factors. The location of the CTO was most frequent in the right coronary artery (45.6%), left anterior descending coronary artery (36.2%), circumflex (17,8%) and left main (0.5%); this distribution was similar to the <75 years group. Compared to patients <75 years, the elderly group had a tendency for less diabetes mellitus and current smokers, as well as higher rates of multivessel coronary disease, chronic kidney disease and prior CABG. Although the occurrence of previous MI was not significantly different, the elderly patients had a lower left ventricular ejection fraction (LVEF). During the procedure, a lower amount of contrast was used in the elderly while other procedure variables were similar to the other group.

Procedural Success

The success rates of CTO revascularization between patients <75 years and the elderly were comparable (69.1% vs 63.8% p=0.12). After a successful procedure stents were implanted in 98% of elderly patients (59% drug-eluting stents) and in 94% of younger patients (66.5% drug-eluting stents). Patients <75 years in whom the CTO revascularization failed, were more often male, more frequently had a prior MI and CABG compared to the successful group. Furthermore, they suffered from more extensive coronary artery disease, had longer occlusion length and had more often complications as coronary perforation and residual dissection. In elderly patients in whom the CTO revascularization failed, had more often a history of prior CABG and a tendency towards lower LVEF. The occlusion length and coronary perforation rate was higher in the context of CTO procedure failure, but similar in the two study groups.

Clinical Outcomes

Table 2 shows long-term clinical event rates after successful and failed CTO PCI in elderly patients and patients <75 years. Figure 1 shows the Kaplan-Meier curve for the combined clinical endpoint in both groups. Median follow-up in this cohort was 890 days (IQR 380-1480 days).

In the elderly, the MACE rate was significantly lower in the group with successful CTO revascularization (25.8% vs. 42.3%, p=0.02); this was mainly driven by a reduction in CABG surgery (0.0% vs. 20.4%, p<0.01). There was no significant interaction between proce-

Table 1. Baseline demographic, angiographic and procedural characteristics of all patients aged <75 years and aged ≥75 years, and of patients aged <75 years and aged ≥75 years stratified according to procedural success.

				Age <75 years			Age ≥75 years		
Variable	**Age <75 years (n=1578, 88.1%)**	**Age ≥75 years (n=213, 11.9%)**	**p-value**	**Successful PCI (n=1090, 69.1%)**	**Failed PCI (n=488, 30.9%)**	**p-value**	**Successful PCI (n=136, 63.8%)**	**Failed PCI (n=77, 36.2%)**	**p-value**
Baseline Characteristics									
Age in years	59.1±8.9	79.0±3.3	<0.01	59.0±9.1	59.4±8.5	0.34	79.1±3.4	78.8±3.3	0.51
Male gender	87.3%	77.9%	<0.01	86.0%	90.2%	0.02	75.7%	81.8%	0.30
Hypertension	59.1%	64.9%	0.11	59.5%	58.2%	0.64	64.3%	65.8%	0.83
Current smoking	27.3%	20.0%	0.08	28.7%	24.2%	0.06	22.5%	15.8%	0.25
Hypercholesterolemia	65.4%	56.3%	0.01	67.3%	62.0%	0.05	58.7%	52.6%	0.41
Diabetes mellitus	23.4%	17.6%	0.06	23.5%	23.1%	0.88	20.2%	13.2%	0.20
Insulin dependent diabetes mellitus	12.9%	11.0%	0.17	12.8%	13.2%	0.66	14.3%	5.3%	0.045
Prior myocardial infarction	49.1%	54.2%	0.18	46.0%	56.5%	<0.01	53.1%	56.0%	0.69
Chronic kidney disease	2.9%	7.4%	<0.01	2.6%	3.4%	0.41	7.0%	8.0%	0.79
Prior coronary artery bypass surgery	15.1%	22.3%	<0.01	13.2%	19.3%	0.01	17.2%	31.2%	0.02
Ejection fraction (%)	53.9±10.1	49.4±10.4	<0.01	54.1±9.9	53.3±10.6	0.18	50.6±11.0	47.2±10.3	0.06
Angiographic and procedural characteristics									
CTO located in			0.34			0.14			0.24
Left anterior descending artery	34.3%	36.2%		35.7%	31.1%		39.7%	29.9%	
Circumflex	23.4%	17.8%		23.9%	22.1%		16.2%	20.8%	
Right coronary artery	41.9%	45.6%		39.9%	46.3%		44.1%	48.1%	
Left main	0.4%	0.5%		0.5%	0.4%		0.0%	1.3%	
Multivessel disease	67.0%	77.7%	<0.01	63.6%	74.4%	<0.01	75.2%	80.3%	0.40

Table 1. Baseline demographic, angiographic and procedural characteristics of all patients aged <75 years and aged ≥75 years, and of patients aged <75 years and aged ≥75 years stratified according to procedural success. (continued)

Variable	Age <75 years (n=1578, 88.1%)	Age ≥75 years (n=213, 11.9%)	p-value	Age <75 years			Age ≥75 years		
				Successful PCI (n=1090, 69.1%)	Failed PCI (n=488, 30.9%)	p-value	Successful PCI (n=136, 63.8%)	Failed PCI (n=77, 36.2%)	p-value
CTO length (mm, per lesion)	23.5±15.3	23.1±15.2	0.84	22.5±15.8	25.9±13.8	0.01	21.1±13.8	28.3±17.6	0.049
Double coronary injection	27.2%	22.5%	0.15	28.5%	24.3%	0.08	22.1%	22.7%	0.91
Residual dissection	5.7%	6.7%	0.57	4.0%	10.1%	<0.01	7.5%	5.3%	0.56
Coronary perforation during procedure	3.4%	3.3%	0.94	1.9%	7.1%	<0.01	0.0%	9.2%	<0.01
Total amount of contrast used (ml)	482±226	404±197	0.01	490±222	437±241	0.08	399±196	417±203	0.73
Reattempts after prior failed PCI	19.0%	21.7%	0.40	n/a	n/a	n/a	n/a	n/a	n/a
Procedural success	69.1%	63.8%	0.12	n/a	n/a	n/a	n/a	n/a	n/a
Number of patients treated with stents	n/a	n/a	n/a	1027 (94%)	n/a		133 (98%)	n/a	
Number of stents per lesion	n/a	n/a	n/a	1.7±1.0	n/a		1.6±0.9	n/a	
Stent length (mm, per stented lesion)	n/a	n/a	n/a	40.9±25.0	n/a		39.5±24.5	n/a	
Stent type									
Bare metal stent	n/a	n/a	n/a	33.2%	n/a		41.4%	n/a	
Sirolimus-eluting stent	n/a	n/a	n/a	48.3%	n/a		44.4%	n/a	
Paclitaxel-eluting stent	n/a	n/a	n/a	18.2%	n/a		14.3%	n/a	
Other drug-eluting stent type	n/a	n/a	n/a	0.3%	n/a		0.0%	n/a	

PCI= percutaneous coronary intervention, CTO= chronic total occlusion

Table 2. Major Adverse Cardiovascular Events at 5 year follow-up after successful versus failed CTO revascularization stratified for age.

	Age <75 years			Age ≥75 years		
Event	Successful PCI (n=1090, 69.1%)	Failed PCI (n=488, 30.9%)	p-value	Successful PCI (n=136, 63.8%)	Failed PCI (n=77, 36.2%)	p-value
MACE	11.2%	20.8%	<0.01	25.8%	42.3%	0.02
CABG	3.6%	12.7%	<0.01	0.0%	20.4%	<0.01
Myocardial infarction	5.1%	5.1%	0.89	11.5%	8.0%	0.87
Mortality	4.4%	6.1%	0.052	19.6%	24.6%	0.13

CABG= coronary artery bypass graft, MACE= major adverse cardiovascular events, PCI=percutaneous coronary intervention.

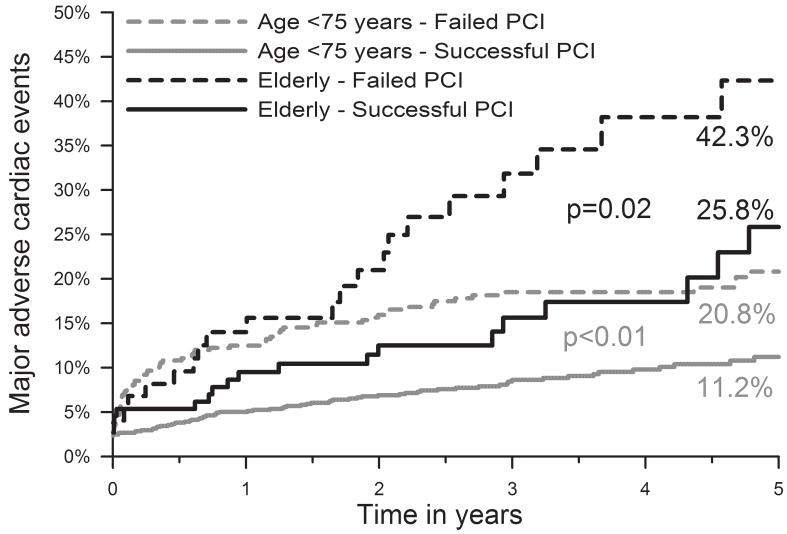

Figure 1. MACE rates at 5 year follow-up for successful versus failed PCI of CTO, stratified for age at 75 years. MACE= major adverse cardiovascular event, PCI= percutaneous coronary intervention, CTO= chronic total occlusion.

dural success and age ≥75 years in terms of MACE (p=0.15). There were no significant differences in terms of mortality (19.6% vs. 24.6%, p=0.13) or MI (11.5% vs 8.0%, p=0.87).

In patients <75 years, the combined MACE rate was also significantly lower after successful PCI (11.2 vs. 20.8%, p<0.01). We observed a statistical trend towards lower mortality after successful PCI (4.4% vs. 6.1%, p=0.052). The occurrence of myocardial infarction was similar (5.1% vs. 5.1%) whereas the need for subsequent CABG surgery was considerably lower in the successful group (3.6% vs 12.7%, p<0.01). In elderly patients, there were only 3 stent thrombosis events, all of them probable very late stent thrombosis events occurring at day 546, day 1070, and day 1659, respectively.

Table 3 shows independent predictors of MACE in elderly and younger patients. Procedural success was independently associated with lower MACE rates in both younger and older patients. Moreover, chronic kidney disease was associated with a higher MACE rate in younger patients and diabetes mellitus was associated with a higher MACE rate in elderly patients.

Table 3. Independent predictors of major adverse cardiovascular events in patients aged <75 years and aged ≥75 years.

Variable	Hazard Ratio	95% Confidence Interval	P-Value
Patients aged <75 years (n=1578)			
Procedural success	0.48	0.35-0.65	<0.01
Chronic kidney disease	2.42	1.31-4.47	0.01
Patients aged ≥75 years (n=213)			
Procedural success	0.45	0.24-0.84	0.01
Diabetes mellitus	2.90	1.50-5.63	<0.01
Overall cohort (n=1791)			
Procedural success	0.49	0.37-0.64	<0.01
Age (per year increment)	1.02	1.003-1.03	0.01
Chronic kidney disease	1.97	1.1-3.4	0.03

DISCUSSION

This analysis from the large multinational CTO registry showed that CTO PCI in patients ≥75 years has similar success as in patients <75 years. In elderly patients, successful revascularization is associated with a reduction in MACE at 5-year follow-up.

Age and PCI-associated Risk

In most randomized controlled trials, patients >75-80 years are often excluded from participation. Additionally, cohort studies often do not focus on this special subgroup. Older patients are considered to have a reduced life expectancy and numerous comorbidities that may contribute to adverse events unrelated to the therapy under investigation. As the proportion of elderly suffering from coronary artery disease is increasing, more studies are needed to guide clinical practice. In general, the risk of adverse outcomes increases with age due to several physiological changes. As confirmed in our study cohort, the MACE rates in the elderly for both the successful and failed group were overall substantially higher compared to patients < 75 years, table 2. Elderly patients are known to have more extensive coronary artery disease, tortuosity and severely calcified atherosclerotic plaques.[12-15] This increases the complexity of percutaneous intervention in the coronary tree and increases the likelihood of peri-procedural complications to develop.[16] Additionally, elderly patients often have multiple comorbidities, including chronic kidney disease, which increases the risks associated with PCI.[17-19] In the current study, elderly patients indeed more often had a history of chronic kidney disease, prior CABG surgery and a lower LVEF; however, these differences did not result in an increased procedural complication rate. This finding, in combination with a comparable success

rate suggests that PCI of CTO is safe in the elderly patient. In our cohort, elderly patients receiving CTO revascularization have a slightly lower rate of some of the traditional cardiovascular risk factors than may be expected. This indicates that our study population represents a selected population of relatively healthy elderly patients with a CTO. This is understandable, as they are a group selected for performance of an invasive cardiac procedure. Accordingly, no data are available on patients who were ineligible to undergo PCI of a CTO and consequently were treated either medically or with CABG. However, our study shows that CTO PCI in the elderly is safe and feasible

Successful versus Failed PCI of CTO

To the best of our knowledge, this is the first observational study reporting the effect of CTO revascularization particularly in elderly patients. The success rate of CTO revascularization was comparable between the elderly and the younger patients, 69.1% vs 63.8% p=0.12. A previous report from the same cohort showed a variation of the annual success rates ranging from 51.4% to 77.1%. There was a statistically significant trend showing that the success rates increased over time (p<0.01). Over the years, technical improvements of wires and catheters in combination with specialized experienced tertiary centers likely improved the ability to cross the CTO lesion.[10]

In previous literature, several beneficial effects of CTO revascularization has been reported, such as improvement of quality of life, exercise capacity, LVEF, electrical stability and reducing the need for subsequent CABG surgery.[5,10,20,21] Moreover, the presence of a CTO in a non-infarct related artery in patients with ST-segment elevation myocardial infarction (STEMI) has associated with increased mortality.[22-25] Therefore revascularization of a CTO may result in better outcomes after a future STEMI. A recently published meta-analysis of 13 retrospective observational studies showed a 44% reduction of mortality in patients with successful CTO revascularization.[7] Until now, clinical outcome of CTO PCI in the elderly was unknown. MACE rates were significantly reduced in the successful group, mostly driven by a less need of CABG surgery. With increasing age, the aim and importance of treating heart disease shifts from lengthening of life to improvement of quality of life and preservation of independence. Several studies have investigated the effect of CABG surgery versus PCI on neurological complications. Detailed neurocognitive testing has shown that up to 60% of elderly patients have short-term cognitive impairment of which 20% long-term.[26,27] Possible explanatory mechanisms could be decreased peri-procedural cerebral perfusion and micro-emboli resulting from manual manipulation of the aorta and great vessels. Other complications associated with CABG surgery in the elderly are e.g.: renal failure, respiratory problems, sepsis and arrhythmia's.[28] Therefore, achieving a significant reduction in CABG surgery by successful CTO PCI may be considered a clinically significant benefit for the elderly population.

The absolute mortality reduction in the elderly was 5%; this was associated with a 20.3% relative risk reduction, whereas the group <75 years of age had only 1.7% absolute risk reduction with a successful PCI which was associated with a 27.9% relative risk reduction and approached statistical significance. We may derive that the elderly group may derive greater absolute mortality reduction if these results are tested and verified in a larger sample. To date, no randomized controlled trial has shown a mortality reduction for PCI vs optimal medical treatment (OMT) in patients with stable coronary artery disease.[29-31] Current literature concerning successful versus failed PCI of CTO suggests that a survival benefit could be present.[7] However, there is no observational study or RCT that compared PCI with OMT alone. While awaiting a number of pending RCTs[32,33], the ACC/AHA guidelines recommend that PCI of CTO is a reasonable treatment option if a clinical indication and suitable anatomy is present (IIa, level B).[34] Our study shows that this recommendation is also valid in elderly patients with cardiac symptoms and or evidence of ischemia in the related territory.

Limitations

Limitations of the multinational CTO registry have been previously published.[10] This study was not a randomized trial but a registry with prospectively collected data from 3 tertiary referral centers around the world. We had no information on earlier CTO attempts in other hospitals. Moreover, no information on fluoroscopy time was available in our database.

CONCLUSION

Current evidence shows that the decision to perform PCI should not be based on age alone but rather on each patient's general eligibility for revascularization and the clinical circumstances as a whole. CTO PCI in patients ≥75 years has similar success as in patients <75 years. In elderly patients undergoing CTO PCI, MACE rates were relatively high but successful revascularization is associated with a reduction in MACE at 5-year follow-up in both elderly and younger patients.

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Chapter 6

Meta-Analysis on the Impact of Percutaneous Coronary Intervention of Chronic Total Occlusions on Left Ventricular Function and Clinical Outcome

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International Journal of Cardiology 2015 Mar;187:90-96

ABSTRACT

Background

Percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) may have a beneficial effect on survival through a better-preserved or improved LVEF. Current literature consist of small observational studies therefore we performed a weighted meta-analysis on the impact of revascularization of CTOs on left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and long-term mortality.

Methods

We conducted a meta-analysis evaluating LVEF before and after CTO PCI and long-term mortality. No language or time restrictions were applied. References from the identified articles and reviews were examined to find additional relevant manuscripts.

Results

Of the 812 citations, 34 studies performed between 1987-2014 in 2,243 patients were eligible for LVEF and 27 studies performed between 1990-2013 in 11,085 patients with successful and 4,347 patients with failed CTO PCI were eligible for long-term mortality. After successful CTO PCI, LVEF increased with 4.44% (95%CI: 3.52-5.35, p<0.01) compared to baseline. In a small cohort of ~70 patients, no significant difference in LVEF was observed after non-successful CTO PCI or reocclusion. Additionally, 8 studies reported the change in left ventricular end-diastolic volume (LVEDV) in a total of 412 patients. LVEDV decreased with 6.14 ml/m^2 (95%CI:-9.31- -2.97, p<0.01). Successful CTO PCI was also associated with reduced mortality in comparison with failed CTO PCI (OR: 0.52, 95%CI: 0.43-0.62,p-value<0.01).

Conclusions

The current meta-analysis revealed that successful recanalization of a CTO resulted in an overall improvement of 4.44% absolute LVEF points, reduced adverse remodeling and an improvement of survival (OR:0.52).

INTRODUCTION

On coronary angiography, a chronic total occlusion (CTO) is observed in approximately 16% of patients with significant coronary artery disease.[1,2] Of these patients, the majority will be treated medically (64%) or are referred for CABG surgery (26%) whereas only 10% will be referred for percutaneous CTO revascularization.[1] The overall conservative approach is somewhat concerning as observational data has shown a possible beneficial effect on clinical outcome after percutaneous coronary intervention (PCI). Numerous beneficial effects have been reported e.g. improvement of angina and quality of life, improvement of electrical myocardial stability, reduced need for CABG surgery, but above all, improved survival.[3-5] It has been hypothesized that the underlying mechanism primarily accountable for this effect is an improved or better preserved left ventricular function (LVF).[6] Current literature contains several reports addressing the effect of CTO PCI on left ventricular ejection fraction (LVEF) though they are mostly small observational studies which could under- or overestimate the true effect. For this reason, we decided to perform a meta-analysis of the literature describing the impact of CTO PCI on LVEF that has never been reported before (references reported in appendix 1). Furthermore, we will update the most recent meta-analyses on long-term survival (references reported in appendix 1).[7]

METHODS

Literature search and study selection

This meta-analysis was conducted and reported according to the proposal for conducting and reporting Meta-analyses Of Observational Studies in Epidemiology (MOOSE).[8] A literature search was performed using major databases, including PubMed, the Cochrane Library, and ClinicalTrials.gov website for randomized controlled trials until January 20th 2014 evaluating the impact of successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) on left ventricular function and comparing long-term mortality after successful versus failed CTO PCI. The initial key words were: "chronic total occlusion(s)," "chronic total coronary occlusion(s)", ''chronic", ''occlusion(s)", ''percutaneous coronary intervention", ''angioplasty", ''recanalization", ''revascularization", , "ventricular function," "ventricular contraction", "ejection fraction", and ''successful". No language or time restrictions were applied. References from the initially identified articles and reviews were examined to find additional relevant manuscripts. The titles and abstracts of relevant studies were identified through the data search and reviewed independently by 2 investigators (LPH, BEC) to determine whether they met the eligibility criteria for inclusion. Discrepancies regarding whether to include or exclude

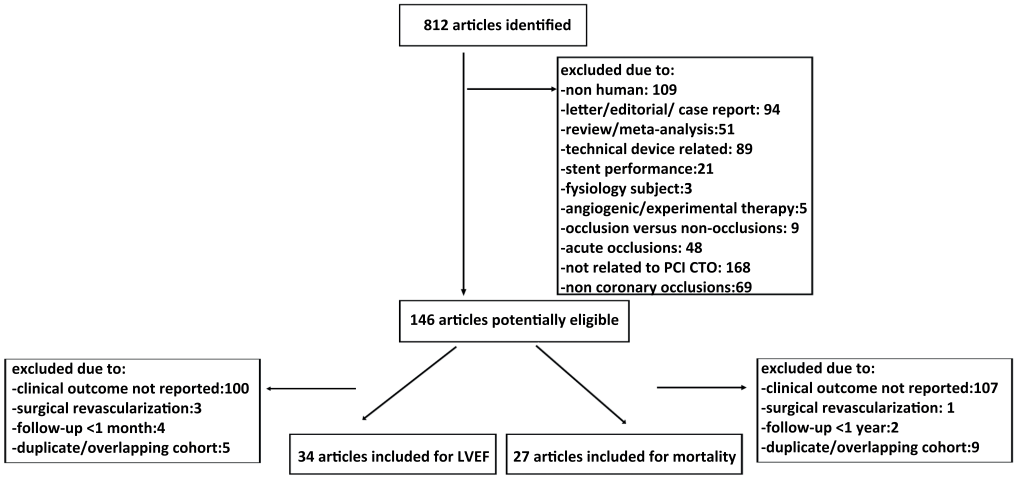


Figure 1. Flow diagram of studies included in the meta-analysis.

a study were resolved by consensus with the other co-authors. To be included for the meta-analysis on left ventricular function, studies had to include patients with a chronic occlusion who received successful revascularization by percutaneous intervention only and the left ventricular function needed to be assessed before revascularization and after at least 1 month of follow-up. For the meta-analysis on long-term mortality, studies had to include patients with a chronic occlusion who were compared according to the successfulness of the percutaneous intervention and reported on all-cause mortality or when absent, cardiac mortality, at ≥1 year after the index procedure. To prevent patient overlap, only the latter study was included in the final analysis in case multiple separate studies reported on the same patient data and outcomes from a single centre. Figure 1 shows the complete search strategy with inclusion and exclusion criteria.

Data extraction and data analysis

The primary endpoint was the change in left ventricular ejection fraction (LVEF) from baseline to follow-up after successful CTO PCI and long-term mortality after successful versus failed CTO PCI. Initially, all studies reporting on a ''chronic occlusion'' were included in the analysis, regardless of the CTO definition. To prevent distortion of the results by the inclusion of acute or sub-acute 100% occlusions, a subgroup analysis was performed on only those studies that included patients with a CTO of at least 3 months. Furthermore, in this ≥3 months occlusion duration subgroup for the outcome LVEF, studies with a follow-up duration < 4 months were excluded as recovery of LV function in chronically ischemic viable hibernating or stunned myocardium starts within 1 to 4 weeks after revascularization and is usually complete within 3 months.[9,10] When several methods were used for LVEF assessment magnetic resonance (MRI) data were

preferentially included in the analysis, followed by nuclear imaging, echocardiography, and left ventricular (LV) angiography.

The secondary outcomes were change of LVEF after CTO PCI failure, change of LVEF after reocclusion during follow-up and change in left ventricular end-diastolic volume (LVEDV) reported as ml/m^2 to assess the effect on left ventricular remodeling.

For LVEF and LVEDV measurements, we used the reported mean and standard deviation at baseline and follow-up. For mortality, absolute numbers of mortality events were primarily used but when absent they were calculated from the Kaplan-Meier estimates or extracted from the survival curves. When reported or published data were incomplete, we requested additional details by correspondence or calculated or estimated the missing data using the method of the Cochrane handbook.[11] In case of an intervention or experimental study, only the control group was included.

Statistical analysis

For the outcomes LVEF and LVEDV, summary results were presented as weighted mean difference with 95% CI. For the outcome long-term mortality, summary results were presented as odds ratios (OR) with 95% CI. We examined heterogeneity across studies by calculating an I^2-value for every outcome. A standard fixed-effects model (Mantel–Haenszel method) was used in the absence of heterogeneity among studies (I^2 value less than 25%). In the presence of heterogeneity, the DerSimonian and Laird random effects model was used.

Potential publication bias was assessed by visual assessment of constructed funnel plots (appendix 2). Tests were two-tailed and a P-value of 0.05 was considered statistically significant. All analyses were performed using Review Manager 5.2.

RESULTS

Of the 812 citations 666 were initially excluded after screening at the title and abstract level (figure 1). Of the remaining 146 studies, a total of 34 were eligible for inclusion in the meta-analysis on left ventricular function (references reported in appendix 1). We did not find any randomized controlled trials between CTO PCI versus medical treatment only. The study and patient characteristics are presented in table 1. These trials were published between 1987-2014 and included 2,310 CTO patients, ranging from 14-290 participants per trial, who underwent successful CTO PCI in whom LVEF was evaluated before and after CTO revascularization. The follow-up duration varied from 1 to 36 months. Improvement of LVEF within 36 months in patients receiving successful CTO PCI was significantly augmented compared to baseline with a pooled estimate of 4.44% (95% confidence interval (CI): 3.52-5.35, p<0.01,figure 2. In the subgroup of studies

Table 1. Characteristics of included studies and patients evaluating LVEF before and after successful CTO PCI.

Study	year	n	CTO definition	Imaging modality for LVF assessment	Follow-up (months)	Age (years)	Men (%)	Previous MI (%)	DM (%)	MVD (%)	Stent (%)	DES (%)
Chen [1]	2009	132	≥ 3 months TIMI 0	NA	12	64 (15)	74	46	26	85	100	96
Cheng [2]	2008	15	≥3 months, TIMI 0-1	MRI	6	65 (3)	82	29	24	NA	NA	87
Chung* [3]	2003	75	≥3 months, TIMI 0	LV-angio	5.9	67 (9)	81	59	41	NA	85.3	NA
Danchin* [4]	1996	55	≥10days, TIMI 0	LV-angio	6	55 (10)	76	60	NA	NA	NA	NA
Daniłowicz-Szymanowicz [5]	2014	23	>4 weeks	echo	3	55 (8)	70	61	43	0	100	0
Dzavik [6]	2001	139	> 6 weeks, TIMI 0-1	LV-angio	6	NA	NA	NA	NA	NA	NA	NA
Engelstein* [7]	1994	49	>3 weeks,TIMI 0-1	LV-angio	2.5	53 (11)	84	59	NA	25	NA	NA
Erdogan [8]	2013	118	>3 months,TIMI 0-1	echo	1	58 (9)	82	NA	36	NA	100	100
Ermis [9]	2005	19	≥6 weeks, complete occlusion	Nuclear scan	1.5	58 (5)	84	84	11	NA	100	NA
Fang [10]	2005	129	≥6 weeks, TIMI 0	LV-angio	6	66 (12)	73	37	42	74	48	NA
Fettser [11]	2011	95	>1 month, TIMI 0	echo	6	57 (11)	83	63	20	NA	100	0
Fiocchi [12]	2009	14	≥3 months, complete occlusion	MRI	6	65 (10)	91	65	39	NA	100	100
Gottschall [13]	1997	21	≥1 week, no antegrade flow	LV-angio	6	NA	NA	NA	NA	NA	NA	NA
Heyder [14]	1996	34	≥2 months,TIMI 0-2	LV-angio	1.5-2	NA	NA	NA	NA	NA	NA	NA
Ivanhoe [15]	1992	175	≥10 days TIMI 0-1	LV-angio	6	NA	NA	NA	NA	NA	NA	NA
Jin [16]	2001	64	>2 weeks, TIMI 0	echo	6	61 (13)	66	67	13	77	100	NA
Kirschbaum [17]	2008	21	≥6 weeks, complete occlusion	MRI	36	64 (115)	86	57	14	NA	100	100
Kirschbaum [18]	2012	43	≥3 months	MRI	6	60 (10)	79	54	21	33	100	100
Kux [19]	1989	17	Not stated	LV-angio	3	53 (9)	88	NA	NA	NA	NA	NA
Melchior [20]	1987	20	Not stated	LV-angio	9	53	85	70	NA	NA	NA	NA
Mori †[21]	1996	45	>1 month, TIMI 0-1	LV-angio	6	58 (9)	NA	82	NA	NA	NA	NA
Nii [22]	2007	17	>1 month, TIMI 0	LV-angio	6	66 (12)	82	NA	29	65	100	47
Ogita [23]	2011	48	≥3 months,TIMI 0	LV-angio	6	60 (10)	83	48	40	71	100	92

Table 1. Characteristics of included studies and patients evaluating LVEF before and after successful CTO PCI. (continued)

Study	year	n	CTO definition	Imaging modality for LVF assessment	Follow-up (months)	Age (years)	Men (%)	Previous MI (%)	DM (%)	MVD (%)	Stent (%)	DES (%)
Park [24]	2012	58	>3 months, TIMI 0-1	LV-angio	6	60 (11)	83	12	36	76	100	98
Pavlovic [25]	2009	20	≥3 months, TIMI 0-1	Nuclear scan	11	55 (6)	75	100	33	NA	NA	71
Petrenko [26]	2012	82	Not stated	echo	12	52 (6)	100	88	45	NA	NA	NA
Piscione[27]	2005	35	100% occlusion	echo	6	58 (10	87	100	18	31	100	NA
Pujadas[28]	2013	33	≥3 months, TIMI 0	MRI	6	66 (9.5)	79	39	36	NA	NA	94
Roifman[29]	2013	19	>90 days, TIMI 0-1	MRI	4	62 (10)	74	58	26	NA	100	100
Schacherer [30]	1993	25	Not stated	Nuclear scan	4	55 (8)	90	NA	NA	NA	NA	NA
Sirnes* [31]	1998	95	≥2 weeks	LV-angio	6.7	59	77	64	8	42	71	NA
Sun‡ [32]	2012	99	≥3 months	Echo	12	54 (4)	92	65	25	NA	100	100
Valenti [33]	2008	290	≥3 months TIMI 0	Echo	6	NA	NA	NA	NA	NA	100	100
Werner [34]	2005	119	≥2 weeks, TIMI 0	LV-angio	4.9	64 (10)	NA	65	31	57	100	NA

Abbreviation: CTO: chronic total occlusion, DM: diabetes mellitus, DES: drug eluting stent, LVEF: left ventricular ejection fraction, NA: not available, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction. *only included LAD and RCA CTO locations, †only occluded pt with LVEF <55%, ‡ only included CTO located in LAD. References in appendix 1.

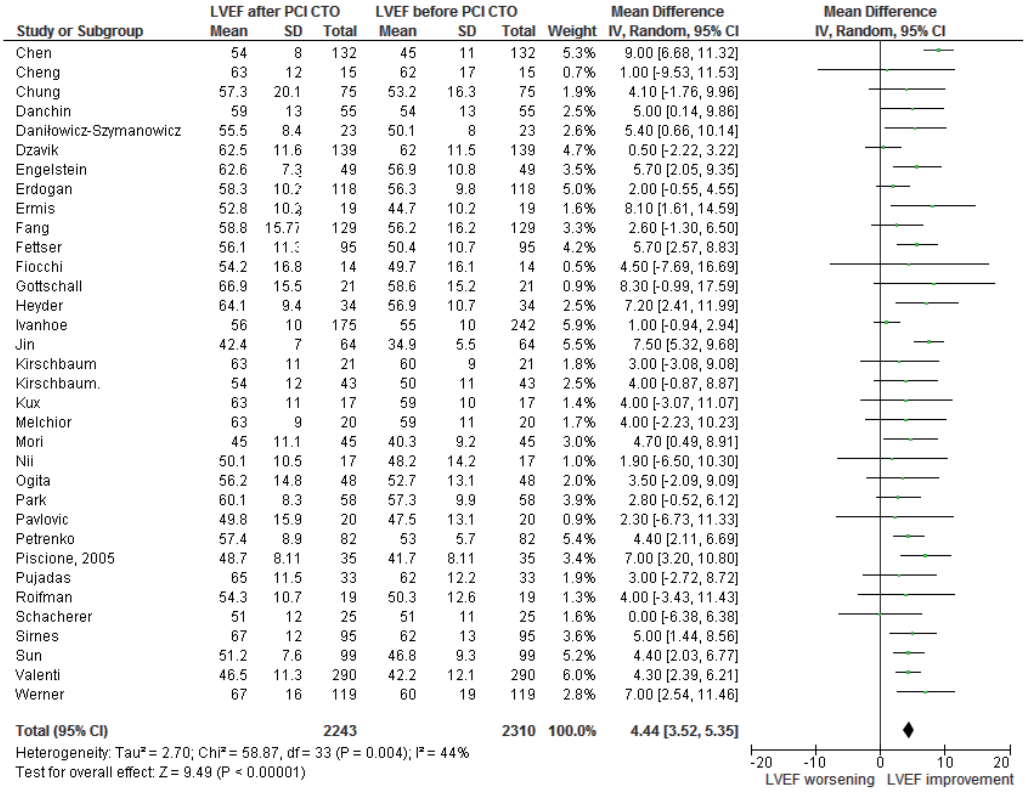
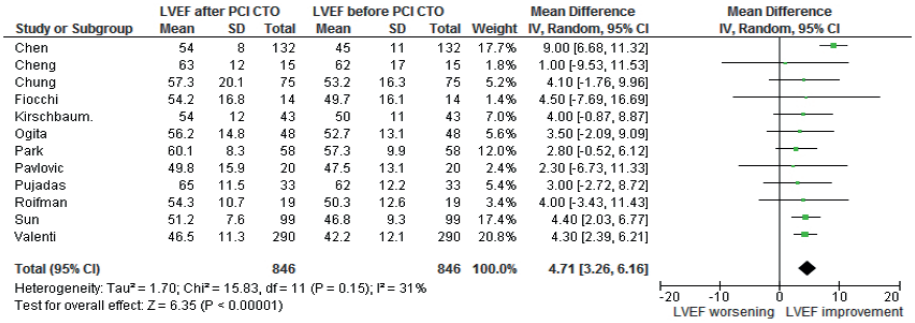


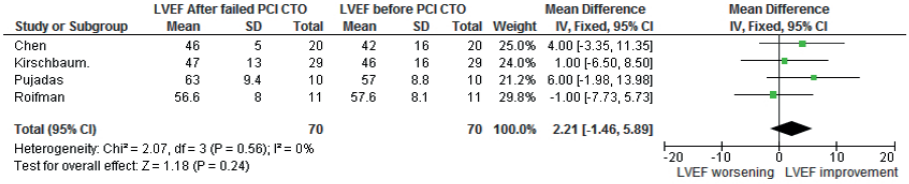
Figure 2. Meta-analysis of studies evaluating the effect of successful CTO revascularization on LVEF.
The meta-analysis shows effect estimates for the individual trials and for the overall analysis. The size of each square is proportional to the weight of the individual trial. The results are presented as mean LVEF difference after versus before successful CTO PCI.
Abbreviations: CTO: chronic total occlusion, LVEF: left ventricular ejection fraction and PCI: percutaneous coronary intervention.

with a CTO duration of at least 3 months and a follow-up duration of at least 4 months, the change in LVF was comparable (4.71% 95% CI: 3.26-6.16, p-value< 0.01), figure 3A. In these studies, the rate of stent implantation was >70% , the majority being drug eluting stents. Only 4 studies evaluated the effect of failed CTO PCI on LVEF, with a small number of participants, ranging from 10-29. In case the CTO procedure failed, a non-significant pooled estimate was observed, figure 3B. Several studies evaluated the impact of reocclusion observed during follow-up angiography after an initial successful CTO procedure. When combined, these studies included 65 patients and showed no difference in LVEF at follow-up compared to baseline (figure 3C). In addition to LVEF, 8 studies reported the change in LVEDV in a total of 412 patients (figure 3D). The LVEDV decreased with 6.14 ml/m^2 (95%CI:-9.31- -2.97, p<0.01), reflecting less adverse remodeling after successful CTO PCI.

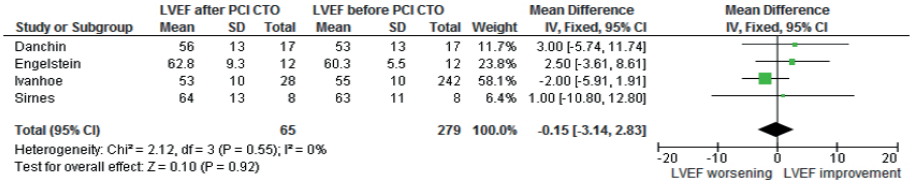
3A. CTO definition of at least 3 months and 4 months follow-up duration.



3B. Failed CTO PCI.



3C. Reocclusion during follow-up after successful CTO PCI.



3D. Effect on left ventricular end-diastolic volume.

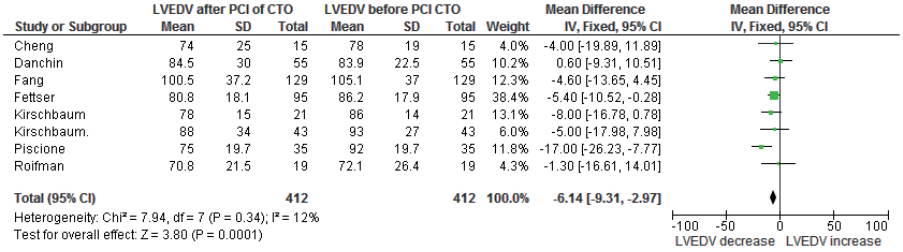


Figure 3. Meta-analysis of several subgroups evaluating the effect of CTO revascularization on LVEF.
The meta-analysis shows effect estimates for the individual trials and for the overall analysis. The size of each square is proportional to the weight of the individual trial. 3A, shows the results for studies who defined a CTO as >3 months with a follow-up duration of >4 months. 3B, shows the results of studies evaluating the change of LVEF after a failed CTO procedure. 3C, shows the results for studies evaluating the effect of reocclusion during follow-up on LVEF. Ivanhoe et al did not report the separate baseline LVEF of the subsequently reoccluded CTO patients of the successful group, therefore the mean of the whole successful group at baseline was used instead. 3D, shows the results for studies evaluating the change in LVEDV after successful CTO revascularization. The results are presented as mean differences after versus before successful CTO PCI. Abbreviations: CTO: chronic total occlusion, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction and PCI: percutaneous coronary intervention.

Table 2. Characteristics of included studies and patients evaluating Long term mortality after successful versus failed PCI of CTO.

Study	year	CTO definition	N		Follow-up (years)	Age S (years) mean/SD	Age F (years) mean/SD	Men S(%)	Men F(%)	Previous MI S(%)	Previous MI F(%)	DM S(%)	DM F(%)	MVD S (%)	MVD F (%)	Stent S(%)	Stent F(%)	DES S(%)	DES F(%)
			Success	Failed															
Angioi[35]	1995	≥10 days TIMI 0	93	108	3.6	55 (10)	56 (11)	52	88	54	66	10	11	37	45	NA	NA	NA	NA
Arslan[36]	2006	Not defined	117	115	2.7	61 (10)	60 (11)	75	75	40	45	75	26	67	70	92	NA	0	NA
Aziz[37]	2007	≥3 months TIMI 0-1	377	166	1.7	59	59	76	81	58	58	14	9	50	60	98	NA	17	NA
Borgia[38]	2012	≥3 months TIMI 0	237	65	4	64 (10)	65 (11)	82	82	58	60	26	31	73	83	100	NA	100	NA
Chen [1]	2009	≥3 months TIMI 0	132	20	3	64 (15)	68 (7)	74	80	46	65	26	25	85	95	96	NA	100	NA
de Labriolle[39]	2008	≥3 months TIMI 0	127	45	2	61 (12)	64 (10)	72	78	21	22	19	41	45	66	94	NA	84	NA
Drozd[40]	2006	≥1 month TIMI 0-1	280	149	2	57 (10)	58 (10)	81	80	66	73	11	11	46	53	100	NA	0	NA
Finci[41]	1990	NA, TIMI 0	100	100	2	55 (11)	55 (12)	93	88	NA	NA	NA	NA	24	23	NA	NA	NA	NA
Hoye[42]	2005	≥1 month TIMI 0-1	567	304	4.5	60 (11)	61 (10)	74	72	56	49	12	9	54	67	81	NA	0	NA
Ivanhoe[15]	1992	≥10 days TIMI 0-1	317	163	4	55 (10)	56 (11)	81	82	56	53	10	15	30	54	NA	NA	NA	NA
Jaguszewski[43]	2012	≥30 days TIMI 0-1	247	139	2	61 (10)	62 (10)	69	80	45	50	19	16	40	55	100	NA	NA	NA
Jolicoeur[44]	2012	>7 days TIMI 0-1	213	133	5.6	58	61	70	79	21	29	33	26	60	69	100	NA	52	NA
Jones[45]	2012	≥3 months TIMI 0	582	254	3.8	62(12	64(11)	76	79	32	36	27	29	45	49	97	NA	76	NA
Lee[46]	2011	≥3 months TIMI 0	251	82	3.6	59 (10)	64(9)	77	23	18	29	31	30	51	55	100	NA	100	NA
Mehran[47]	2011	≥3 months TIMI 0	1,26	565	2.9	61 (11)	62 (10)	85	89	47	56	23	22	65	75	95	NA	66	NA
Niccoli[48]	2012	≥3 months TIMI 0	196	121	3.2	64 (11)	66 (10)	82	88	32	26	34	37	58	78	100	NA	100	NA
Noguchi[49]	2000	≥3 months TIMI 0	134	92	4.3	61 (9)	61(11)	78	80	36	51	26	32	47	67	NA	NA	NA	NA
Olivari[50]	2003	≥30 days TIMI 0-1	289	87	1	58 (10)	59 (11)	86	85	69	69	17	20	45	60	90	NA	0	NA
Prasad[51]	2007	≥3 months 100% occlusion	914	348	10	63 (11)	64 (11)	76	75	33	42	NA	NA	45	60	NA	NA	NA	NA
Sathe[52]	1994	≥10 days TIMI 0-1	116	62	5.5	55	57	66	70	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Suero[53]	2001	≥7 days TIMI 0-1	1,491	514	7.6	60(11)	61(12)	78	80	56	52	21	20	73	82	7	NA	NA	NA
Tanaka[54]	2013	≥3 months TIMI 0	231	53	3.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Valenti[33]	2008	≥3 months TIMI 0	344	142	2	67 (11)	70 (11)	81	83	45	54	24	21	85	87	100	NA	100	NA
Warren[55]	1990	≥1 week, TIMI 0	26	18	2.6	54	55	53	47	60	40	NA	NA	38	61	NA	NA	NA	NA
Yamamoto[56]	2013	>1 month TIMI 0-1	1,192	332	~2.5	67 (11)	66 (11)	78	76	32	24	42	42	72	83	100	NA	78	NA
Yang[57]	2013	100% occlusion	87	49	2	66 (11)	69 (10	82	82	26	33	36	37	100	100	100	NA	100	NA
Yi X[58]	2009	≥3 months TIMI 0-1	1202	130	6.3	58 (10)	58 (11)	82	84	54	57	18	20	42	48	NA	NA	NA	NA

Abbreviation: CTO: chronic total occlusion, DM: diabetes mellitus, DES: drug eluting stent, NA: not available, PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction. References in appendix 1.

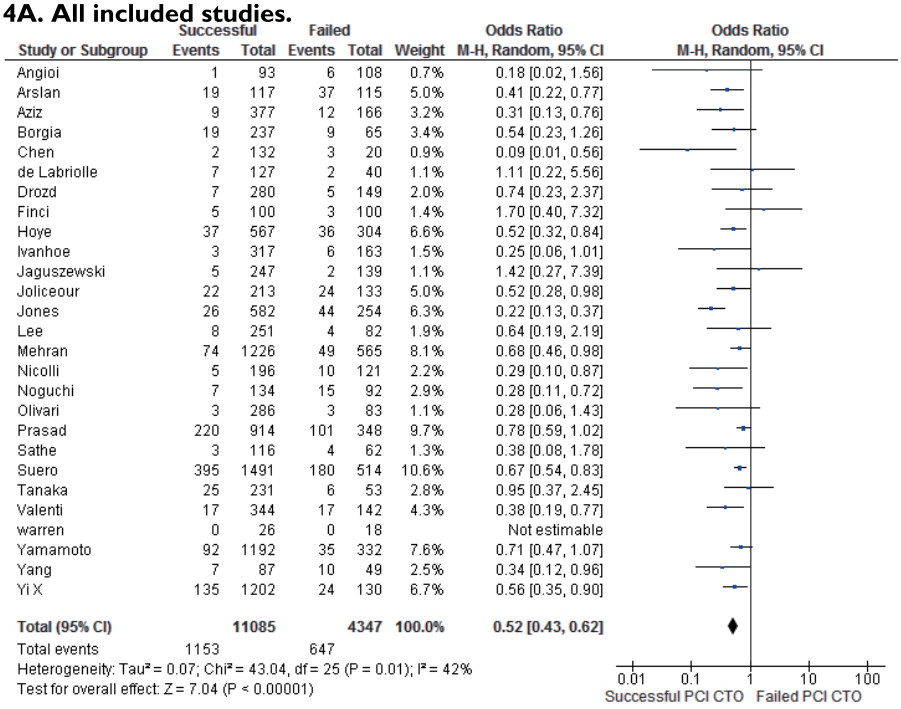


Figure 4. Meta-analyses of studies evaluating successful versus failed CTO revascularization on long-term mortality.

The meta-analysis shows the effect estimates for the individual trials and for the overall analysis. The size of each square is proportional to the weight of the individual trial. The results are presented as odds ratios for mortality after successful versus failed CTO PCI. Figure 4A represents all included studies. Figure 4B shows the studies with a CTO defined as >3 months. Abbreviations: CTO: chronic total occlusion and PCI: percutaneous coronary intervention.

For LVEF the statistical heterogeneity measured by I^2 varied from 44% in the whole cohort, to 0-31% in the several subgroups which probably indicates none to moderate heterogeneity, which is also seen in the 95% confidence intervals of the separate studies which overlap well.[11] Some of the heterogeneity could be explained by the difference in cohort sizes, CTO definition, CTO location, imaging modality and follow-up duration as the heterogeneity is lower in the pre-specified subgroups.

For the meta-analysis on mortality, 27 studies were eligible for inclusion; see figure 1 and table 2 (references reported in appendix 1). We did not find any randomized controlled trials between CTO PCI versus medical treatment only. These studies were published between 1990-2013 and included 11,085 CTO patients with successful CTO PCI and 4,347 CTO patients with unsuccessful revascularization, ranging from 44-2005 participants per study. The follow-up duration varied from 1 to 10 years. Successful CTO PCI was associated with reduced mortality in comparison to failed CTO PCI (OR: 0.52, 95%CI: 0.43-0.62,p-value<0.01), figure 4A. For the subgroup of CTOs with an estimated duration ≥3 months, the results remained qualitatively similar (OR: 0.47, 95%CI: 0.35-0.64, p-value < 0.01), figure 4B.

For mortality, the statistical heterogeneity measured by I^2 ranged from 42% in the whole cohort to 61% in the subgroup analysis which indicate that moderate to substantial heterogeneity could be present although the 95% confidence intervals are overlapping reasonably well. [11] Possible explanations could be the variability in cohort sizes, but also the low number of patients with a failed versus successful CTO PCI, stent usage and moreover difference in follow-up duration..

Assessment of publication bias using visual examination of the funnel plot of the primary publications did not show asymmetry to suggest significant publication bias (appendix 2).

DISCUSSION

For the first time, a weighted meta-analysis was performed to address the change in LVEF and LVEDV after successful CTO revascularization. After successful CTO PCI, the LVEF of the included patients increased with 4.44% while the LVEDV was reduced by 6.14ml/m^2, reflecting less adverse remodeling. These beneficial effects could be related to the observed reduced mortality (OR: 0.52) after successful versus failed CTO PCI.

It is of importance that the overall beneficial effect on LVEF disappeared upon reocclusion of the successfully treated CTO, which was not seen after restenosis. This is in agreement with the non-significant increase of 2.21% LVEF after a failed CTO procedure, with also wide and overlapping 95% confidence intervals. However, the available LVEF data in the reocclusion and failed CTO procedure groups were very scarce and therefore

no hard conclusions can be deducted. The positive non-significant change compared to baseline could be explained by the definition of unsuccessful CTO PCI which was thrombolysis in myocardial infarction flow grade < 3 and a residual diameter stenosis >20-30%. This definition would apply to completely failed procedures resulting in a closed vessel or a partially failed procedure with less than complete failure or just a completely patent, but stenosed vessel. Therefore, it can also be seen as an intermediate effect. This could be reflected by the pooled estimate of the failed group, which is in between the reoccluded and successful group value with also overlapping 95% CI. As a result, the beneficial effect of a persistently patent recanalized CTO lesion may even be larger than estimated in the whole group. Furthermore, besides the beneficial effect of successful CTO PCI on LVEF a favorable effect was found on LVEDV, indicating less adverse remodeling.

Patients with a CTO are associated with worse clinical outcome compared with CAD patients without a CTO. Patients with a CTO more often have previous myocardial infarction (MI), worse left ventricular function and higher mortality.[1,12,13] This meta-analysis confirmed previous findings of a reduced mortality after successful versus failed CTO PCI and theoretically supports the possible relation to LVF.[7,14]

Previous literature has shown that patients with impaired LVF and coronary artery disease (CAD) are prone for sudden cardiac death (SCD) due to ventricular tachyarrhythmia's.[15-17] Retrospective data in patients with ischemic cardiomyopathy and a reduced LVF showed that ICD patients with a CTO more often have therapeutic shocks compared with ICD patients without a CTO.[4] SCD may be prevented by the ICD but the arrhythmogenic substrate remains untreated.[4,5] This substrate consists of ischemia at the border zone of the previous MI and re-entry circuits. As the myocardial territory of a CTO is a persistent ischemic zone,[18] alleviation of ischemia by restoring complete anterograde flow can reduce associated cardiac arrhythmia's. Therefore, besides myocardial salvage, the patency of a previously chronic occlusion may improve survival through other mechanisms such as reduced left ventricular dilation or adverse remodeling preventing heart failure. This coincides with the finding that the most pronounced increase was observed in patients with severely depressed LV function at baseline.[19-21]

The trials included in the meta-analyses contained patients in whom the majority experienced anginal symptoms and or ischemia on non-invasive testing, which is only present when the myocardium is still viable. Werner et al showed that the majority of symptomatic CTO patients with collateral circulation experience ischemia during exercise due to inadequate perfusion distal of the occlusion.[18,21] Kirschbaum et al showed that patients with a transmural extent of infarction (TEI) >75% after contrast enhancement on MRI did not show improved segmental wall thickness after CTO revascularization, opposed to TEI <75%.[22] In a later study, Kirschbaum et al developed a viability score based on several MRI parameters which has a high sensitivity and specificity to

predict improvement of LVF, which can be used as a diagnostic tool.[23] In contrast, Sun et al showed conflicting results.[24] In a small patient cohort with successful CTO PCI of the left coronary artery stratified by the presence of perfusion defects on nuclear imaging before the procedure, both groups with reversible and fixed perfusion defects, showed significant improvement in perfusion abnormalities, LVF and quality of life expressed as improved 6 minute walk distance and frequency of angina. Patients without perfusion defects experienced no improvement. However, a known limitation of nuclear imaging is that even fixed perfusion defects may still show viability on other imaging modalities such as MRI and Positron emission tomography imaging with fluorine 18-deoxyglucose which could also explain this finding.[25-28] Adequately powered randomized controlled trials are needed to address the issue of requirement of viable and ischemic myocardium for improvement of clinical outcome. Although LVEF may not improve, there may still be an effect on LVEDV and electrical stability. Currently, three randomized controlled trials are enrolling patients, namely the EUROCTO (European Study on the Utilization of Revascularization versus Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions) trial , the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) trial and the EXPLORE trial. The latter study is the only one evaluating change in LVEF within and between patients.[29] In this trial, STEMI patients who have been successfully treated with primary PCI and have a concurrent CTO in another coronary artery, will be randomized to PCI within one week or conservative treatment, regardless of viability on the baseline MRI. The primary endpoint is defined as difference in LVEF and LVEDV at 4 months, measured on MRI. Until these trials are completed, current evidence suggest that CTO PCI can result in improved clinical outcome in selected patients and should be seriously considered rather than maintaining a conservative approach.

Limitations. In the included studies measuring change of LVEF, several imaging modalities were used which are different in accuracy. However, in a sensitivity analysis excluding studies who used LV-angiography, the results remained similar (4.79% 95%CI: 3.97-5.62, $p<0.01$). For mortality, patients with successful versus failed PCI were compared. We did not find any literature comparing PCI of CTO with a conservative approach. For this reason, increased mortality rates in the unsuccessful group could be due to negative effect resulting from the failed attempt. However, a recent published meta-analysis showed a comparable safety profile compared to non-CTO PCI.[30] Another limitation is the patient selection due to lack of any randomized data. Patients with failed CTO PCI often have more complex coronary artery disease. For the LVF analysis, the CTO patients were their own control which strengthen our findings as it removes a component of between-person variability from the analysis.

This meta-analysis showed an overall improvement of 4.44% absolute LVEF points after successful CTO PCI. Successful CTO recanalization was also associated with a reduc-

tion of LVEDV by 6.14 ml/m^2 reflecting less adverse remodeling. These findings could be partially responsible for the reduced mortality observed after successful versus failed CTO PCI (OR: 0.52). The data provided in this meta-analysis should be taken into account when considering CTO PCI.

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APPENDIX 1. REFERENCES OF THE INCLUDED STUDIES IN THE META-ANALYSIS

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APPENDIX 2. FUNNEL PLOTS FOR THE EVALUATION OF PUBLICATION BIAS.

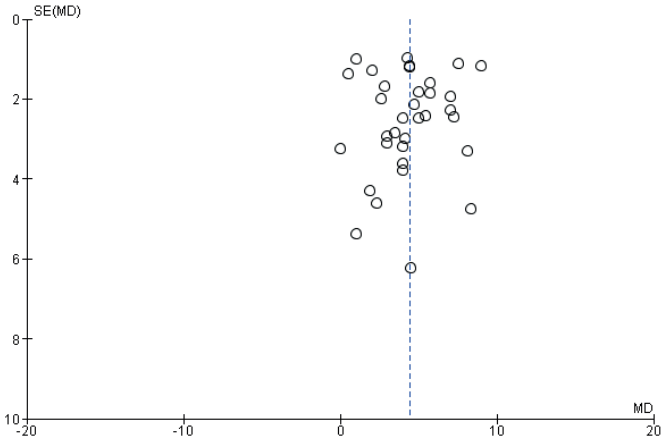

Figure 1. Funnel plot for the evaluation of publication bias for reporting effect of CTO PCI on LVEF.

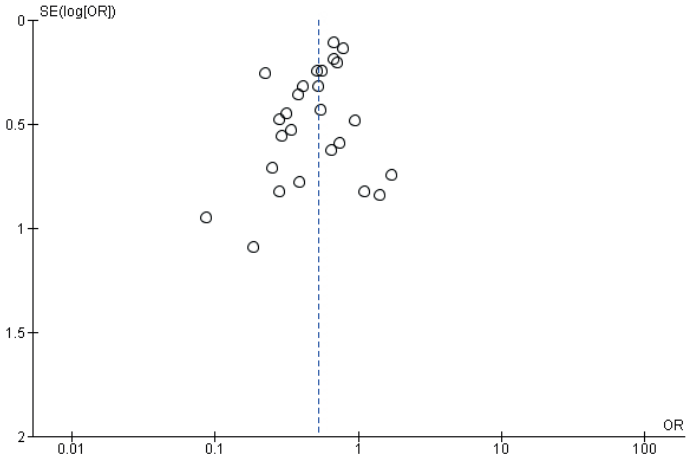

Figure 2. Funnel plot for the evaluation of publication bias for reporting effect of CTO PCI on mortality.

Part III

Chronic total coronary occlusion in acute myocardial infarction

Chapter 7

Impact of a Chronic Total Occlusion in a Non-Infarct Related Artery on Long-Term Mortality in Patients With Diabetes Mellitus after ST-Elevation Myocardial Infarction

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Heart 2010 Dec;96(24):1968-72

ABSTRACT

Background

Recently, a chronic total occlusion (CTO) in a non-infarct related artery (IRA), and not multivessel disease (MVD) alone was identified as an independent predictor of mortality after ST elevation myocardial infarction (STEMI). Patients with diabetes mellitus (DM) constitute a patient group with a high prevalence of MVD and high mortality after STEMI. We studied the prevalence of a CTO in a non-IRA and its impact on long-term mortality in STEMI patients with DM.

Methods

Between 1997 and 2007, we admitted 4506 patients with STEMI treated with primary PCI. Patients with DM were identified. We categorized patients as having single vessel disease (SVD), MVD without CTO and CTO based on the angiogram before PCI.

Results

A total of 539 patients (12%) had DM. Multivessel disease with or without a CTO was present in 33% of nondiabetic patients and in 51% of diabetic patients. The prevalence of a CTO in a non-IRA was 21% in STEMI patients with DM compared to 12% in STEMI patients without DM ($p<0.01$). Kaplan-Meier estimates for 5-year mortality in STEMI patients with DM were 25%, 21% and 47% in patients with SVD, MVD without a CTO and MVD with a CTO in a non-IRA, respectively. A CTO in a non-IRA was an independent predictor of 5-year mortality (Hazard ratio 2.2, 95% confidence interval 1.3-3.5, $p<0.01$).

Conclusion

The prevalence of a CTO in a non-IRA was increased in STEMI patients with DM. The presence of a CTO in a non-IRA was a strong and independent predictor of 5-year mortality. These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.

INTRODUCTION

Patients with diabetes mellitus (DM) constitute a patient group with a high prevalence of multivessel disease (MVD) and high mortality after ST elevation myocardial infarction (STEMI). Approximately 35-45% of nondiabetic STEMI patients have MVD compared with 60-70% of patients with DM. The higher mortality of STEMI patients with DM has been suggested to be, at least partly, due to the greater extent of coronary artery disease.[1-3]

Recently, the presence of a chronic total occlusion (CTO) in a non-infarct-related artery (non-IRA), and not MVD alone, was reported to be an independent predictor of mortality after STEMI.[4-6] Given the greater extent of coronary artery disease in diabetic STEMI patients, we hypothesized that the prevalence of a CTO in a non-IRA would be higher in this high-risk subgroup. Moreover, the prognostic impact of a CTO in a non-IRA in diabetic STEMI patients is currently unknown. Therefore, we studied the prevalence and impact of a concurrent CTO on long-term mortality in STEMI patients with DM.

METHODS

Between 1997 and 2007, a total of 4931 consecutive and unselected patients were admitted to our hospital with STEMI. Acute STEMI was diagnosed when patients had symptoms of an acute myocardial infarction lasting 30 minutes to 6 hours, accompanied by an electrocardiogram with ST-segment elevation >1 mm (0,1 mV) in ≥ 2 contiguous leads. Patients were immediately transported to the cardiac catheterization laboratory and underwent immediate coronary angiography with a view to perform primary PCI. PCI was performed by standard techniques, if the coronary anatomy was suitable. All procedural decisions, including device selection and adjunctive pharmacotherapy, such as glycoprotein IIb/IIIa inhibitors, were made at the discretion of the operator. All patients were treated with heparin (5000 IU) and aspirin (500 mg) prior to PCI. If a coronary stent was implanted, ticlopidine or clopidogrel was prescribed according to the guidelines.[7]

Study cohort

Data for the 4931 patients were checked for consistency and completeness. For patients who underwent >1 primary PCI during the study period (n=147), only the first intervention was included in this analysis. Patients treated with rescue PCI for failed intravenous thrombolysis (n=145), patients without confirmed diagnosis of STEMI (n=76) and patients lost to follow-up (n=57) were excluded. The remaining 4506 patients constitute the present study cohort. This cohort has been described before.[8] We subsequently identified patients with an established diagnosis of DM at time of admission from our electronic database for the current analysis.

Definitions

Patients with DM were categorised according to preadmission treatment: either with oral medication or diet controlled (non-insulin dependent DM [NIDDM]) or with insulin (insulin dependent DM [IDDM]). A CTO was defined as a 100% luminal narrowing in a non-IRA before PCI without antegrade flow or with antegrade or retrograde filling through collateral vessels. Multivessel disease was defined as at least 1 stenosis ≥70% in a non-infarct related epicardial artery or a stenosis ≥50% in the left main coronary artery. Shock was defined according to the clinical criteria used in the "SHould we emergently revascularize Occluded Coronaries for cardiogenic shock?" (SHOCK) trial.[9]

Baseline data

All patients undergoing PCI at our institution were prospectively followed. Baseline clinical, angiographic, and procedural information was entered by qualified cardiac catheterization laboratory personnel and interventional cardiologists in a dedicated electronic database.

Follow up

Information on the vital status was obtained from the institutional follow-up database of PCI patients. Patients were surveyed one year after primary PCI using a mailed, self-administered questionnaire. Information on mortality was synchronized with the computerized records from the national population registry (Statistics Netherlands, Voorburg, the Netherlands) and was verified until January 1, 2009. We reviewed the outpatient files and contacted general practitioners by telephone in the case of conflicting or missing data.

Primary outcome

The primary outcome for the present analysis was all-cause five-year mortality.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software, version 17.0 (SPSS, Inc., Chicago, Illinois). Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics between the three groups were tested for significance by the χ^2 test. Statistical significance was defined as a p value <0.05.

Cumulative event-rates of all-cause death were estimated using the Kaplan-Meier method. Follow-up for mortality was censored at the date of last follow-up by checking vital status in the Dutch population registry, or at 5 years, whichever came first. The Log Rank statistic was used to test for significant differences in mortality between the groups. Hazard ratios for all-cause death were calculated using Cox proportional hazard regression analyses after verification of the proportional hazards assumption.

We constructed 2 multivariate Cox regression models. We used a categorical variable consisting of 3 groups to classify patients as having SVD, MVD without CTO or MVD with CTO. The first model included variables for MVD with CTO and MVD without CTO, with SVD as the reference. The second model included variables for MVD with CTO and SVD, with MVD without CTO as the reference. The following covariates were included in both models: age (as a continuous variable, per year increment), male gender, hypertension, smoking, hypercholesterolemia, previous MI, shock, left anterior descending coronary artery-related MI, post PCI TIMI 3 flow, use of glycoprotein IIb/IIIa inhibitors, and stent use. A covariate was allowed in the model if it influenced the model with a likelihood ratio significance level of p<0.10 and removed if its significance level exceeded p=0.15.

Table 1. Baseline characteristics for ST elevation myocardial infarction patients with and without diabetes mellitus.

	Patients without Diabetes Mellitus	Patients with Diabetes Mellitus	P-value
	n= 3967 (88%)	n= 539 (12%)	
Baseline characteristics			
Male	73%	63%	<0.01
Age >60 years	49%	66%	<0.01
Hypertension	28%	50%	<0.01
Smoker	45%	32%	<0.01
Hypercholesterolemia	20%	33%	<0.01
Family history of cardiovascular disease	40%	33%	<0.01
Previous myocardial infarction	12%	23%	<0.01
Shock	7.6%	10%	0.04
Left ventricular ejection fraction <40%*	16%	25%	<0.01
Angiographic characteristics			
LAD related myocardial infarction	44%	44%	0.86
MVD	33%	51%	<0.01
MVD without CTO	21%	30%	<0.01
MVD with CTO	12%	21%	<0.01
Post-Procedural TIMI flow grade 3	88%	87%	0.23
Procedural characteristics			
Thrombosuction performed	32%	25%	<0.01
Intra-aortic balloon pump	8.4%	11%	0.04
Stent placement	75%	69%	<0.01
Glycoprotein IIb/IIIa inhibitor used	26%	26%	1

* Left ventricular ejection fraction was available for 1844/4506 patients.
LAD= Left anterior descending coronary artery, MVD= Multivessel Disease, CTO= Chronic total Occlusion, TIMI= Thrombolysis in Myocardial Infarction.

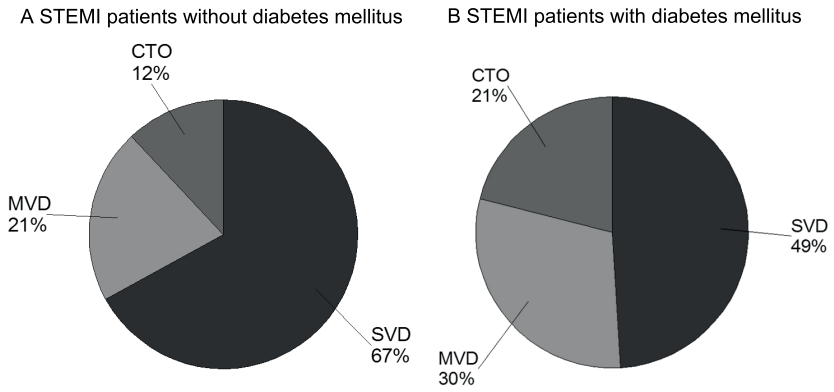

Figure 1. Prevalence of single vessel disease, multivessel disease without a CTO and CTO in (A) patients with STEMI without diabetes mellitus and (B) patients with STEMI with diabetes mellitus. CTO, chronic total occlusion; MVD, multivessel disease (without CTO); STEMI, ST elevation myocardial infarction; SVD, single vessel disease.

RESULTS

Between 1997 and 2007 we treated 4506 STEMI patients with primary PCI of whom 539 (12%) had a confirmed diagnosis of DM at admission. Table 1 shows baseline, angiographic and procedural characteristics for 4506 STEMI patients with and without DM. Patients with DM were older, more often female, and more often had a previous MI and cardiogenic shock at presentation. Furthermore, 51% of patients with DM had MVD compared to 33% of patients without DM ($p<0.01$). Interestingly, the prevalence of a CTO in a non-IRA was 21% in STEMI patients with DM compared to 12% in patients without DM ($p<0.01$)(figure1).

Baseline, angiographic and procedural characteristics for the study cohort of 539 patients with DM are shown in table 2. Diabetic patients with MVD (both with and without a CTO) were older, more often had a previous MI and cardiogenic shock at presentation, were more often treated with IABP counterpulsation, and were less frequently treated with coronary stents and thrombosuction, compared with patients with SVD. Furthermore, patients with a CTO in a non-IRA more often had a previous MI and cardiogenic shock at presentation compared to MVD patients without a CTO.

Kaplan-Meier estimates of 5-year mortality were 18% and 28% in STEMI patients without and with DM, respectively. Figure 2 shows the Kaplan-Meier estimates of cumulative mortality up to 5 years for non-diabetic (2a) and diabetic (2b) STEMI patients with SVD, MVD without a CTO and CTO. In STEMI patients without DM, mortality increased significantly with increasing severity of coronary artery disease. In patients with DM, mortality was significantly higher in patients with a CTO in a non-IRA when compared

to patients with SVD or MVD without a CTO (p<0.01), but there was no significant difference in mortality between patients with MVD without a CTO and patients with SVD (p=0.82). Table 3 shows unadjusted and adjusted hazard ratios of significant predictors of 5-year mortality in STEMI patients with DM. When SVD was used as the reference category, a CTO in a non-IRA was a strong and independent predictor of 5-year mortality (adjusted hazard ratio 2.2, 95% confidence interval 1.3-3.5, p<0.01), whereas MVD without a CTO was not associated with increased 5-year mortality. When MVD without a CTO was used as the reference category, CTO in a non-IRA remained an independent predictor of 5-year mortality (adjusted hazard ratio 2.6, 95% confidence interval 1.6-4.4, p<0.01).

Table 2. Baseline clinical, angiographic and procedural characteristics for 539 ST-elevation myocardial infarction patients with diabetes mellitus.

	SVD	MVD (without CTO)	CTO	P-value
	n=264 (49%)	n=162 (30%)	n=113 (21%)	
Baseline characteristics				
Male	160 (61)	104 (64)	77 (68)	0.36
Age >60 years	153 (58)	121 (75)	82 (73)	<0.01
Hypertension	137 (52)	83 (51)	53 (47)	0.66
Insulin dependent diabetes mellitus*	74 (28)	49 (30)	42 (37)	0.21
Smoker	90 (34)	47 (29)	37 (33)	0.55
Hypercholesterolemia	82 (31)	54 (33)	43 (38)	0.42
Family history of cardiovascular disease	98 (37)	56 (35)	25 (22)	0.02
Previous myocardial infarction	32 (12)	36 (22)	59 (52)	<0.01
Shock	15 (5.7)	16 (9.9)	25 (22)	<0.01
Left ventricular ejection fraction <40%§	23 (22)	17 (28)	11 (31)	0.44
Angiographic characteristics				
LAD related myocardial infarction	128 (49)	64 (40)	45 (40)	0.12
Post-Procedural TIMI flow grade 3	231 (88)	144 (89)	91 (81)	0.11
Procedural characteristics				
Thrombosuction performed	86 (33)	30 (19)	20 (18)	<0.01
Intra-aortic balloon pump	13 (5)	17 (11)	30 (27)	<0.01
Stent placement	196 (74)	106 (65)	71 (63)	0.04
Glycoprotein IIb/IIIa inhibitor used	70 (27)	39 (24)	31 (27)	0.79

*As compared to non-insulin dependent diabetes mellitus, §Left ventricular ejection fraction data were available for 202/539 patients. SVD= Single vessel disease, MVD= Multivessel disease, CTO= Chronic Total Occlusion, LAD= Left anterior descending coronary artery, TIMI= Thrombolysis in myocardial infarction.

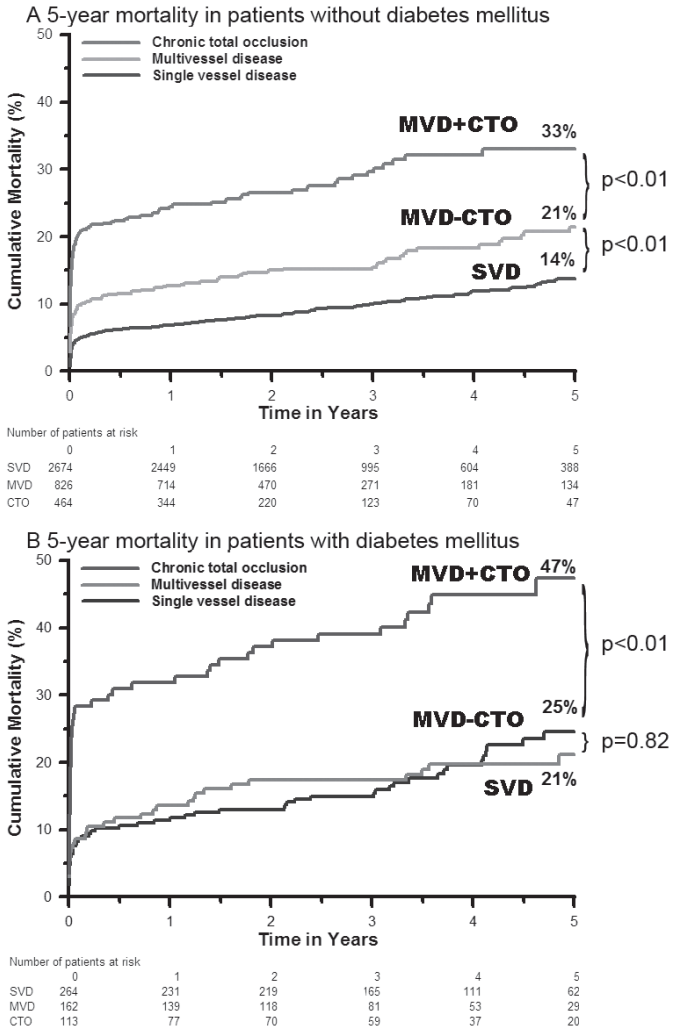

Figure 2. Kaplan-Meier estimates of 5-year mortality in patients with ST elevation myocardial infarction treated with primary percutaneous coronary intervention. (A) Kaplan-Meier estimates for 5-year mortality in ST elevation myocardial infarction patients without diabetes mellitus.(B) Kaplan-Meier estimates for 5-year mortality in ST elevation myocardial infarction patients with diabetes mellitus. CTO, chronic total occlusion; MVD, multivessel disease (without CTO); SVD, single vessel disease.

Table 3. Unadjusted and adjusted significant predictors of 5-year mortality in ST-elevation myocardial infarction patients with diabetes mellitus.

	Unadjusted			Adjusted		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Shock	4.6	3.1-6.8	<0.01	3.6	2.4-5.6	<0.01
CTO (reference SVD)	3.0	2.0-4.6	<0.01	2.2	1.3-3.5	<0.01
CTO (reference MVD without CTO)	3.0	1.9-4.9	<0.01	2.6	1.6-4.4	<0.01
MVD without CTO* (reference SVD)	1.0	0.6-1.6	0.99	0.8	0.5-1.3	0.42
SVD† (reference MVD without CTO)	1.0	0.6-1.6	0.99	1.2	0.7-2.0	0.43
Insulin dependent diabetes mellitus‡	1.4	1.0-2.0	0.04	1.8	1.2-2.6	0.01
Age (per year increment)	1.03	1.01-1.05	<0.01	1.03	1.01-2.05	<0.01
Previous myocardial infarction	1.5	1.1-2.1	0.02			NS
Smoking	0.7	0.4-1.0	0.04			NS
Hypertension	0.6	0.4-0.9	<0.01	0.7	0.5-0.9	<0.01
Stenting	0.5	0.4-0.8	<0.01	0.5	0.3-0.7	<0.01
Post procedural TIMI 3 flow	0.3	0.2-0.4	<0.01	0.4	0.3-0.7	<0.01

*MVD without CTO was forced into the multivariate model with SVD as reference.
†SVD was forced into the multivariate model with MVD without CTO as reference.
‡Compared with non-insulin-dependent diabetes mellitus.
CTO, chronic total occlusion; MVD, multivessel disease; SVD, single vessel disease; TIMI, thrombolysis in myocardial infarction.

DISCUSSION

In this cohort of 4506 STEMI patients of whom 539 patients had DM, the prevalence of a CTO in a non-IRA was almost twice as high in diabetic patients compared to non-diabetic patients. Moreover, a CTO in a non-IRA was a strong and independent predictor of mortality in STEMI patients with DM. This is the first study to evaluate the prevalence and prognostic value of a CTO in a non-IRA in diabetic STEMI patients.

Even with contemporary mechanical reperfusion therapy mortality after STEMI in patients with DM remains high. Diabetic patients are older, have a higher prevalence of co-morbidities and more often have a history of a previous MI.[1,10,11] Nevertheless, the increased risk associated with DM persists after multivariate adjustment. A number of factors may cause the increased morbidity and mortality after STEMI in diabetic patients. Patients with DM are known to have higher rates of incomplete ST-segment resolution and reduced myocardial blush grade after primary PCI for STEMI, suggesting impaired reperfusion at the myocardial tissue level.[12,13] Furthermore, longstanding hyperglycemia, hyperinsulinemia, and increased circulating free fatty acids induce adverse metabolic changes in the endothelium.[14,15] Diabetes mellitus is also associated

with intrinsic myocardial dysfunction, probably as a result of autonomic neuropathy and microvascular dysfunction.[16,17]

This study confirms and extends previous reports showing that patients with diabetes mellitus have more severe coronary artery disease, i.e. a higher prevalence of MVD. Interestingly, we observed that the prevalence of a CTO in a non-IRA was twice as high in STEMI patients with DM compared with patients without DM.

A CTO in a non-IRA has previously been reported to be a predictor of both short- and long-term mortality after STEMI treated with primary PCI.[4-6] Furthermore, a CTO in a non-IRA was associated with reduced LVEF during the index hospitalization and a further reduction in LVEF within the first year thereafter.(4) We recently showed that mortality in STEMI patients with cardiogenic shock and MVD is mainly driven by the presence of a CTO in a non-IRA.[6] Interestingly, in the present study, diabetic patients with MVD without a CTO had a 5-year mortality rate which was comparable to diabetic patients with SVD and comparable to non-diabetic patients with MVD without a CTO.

Moreover, in our multivariate Cox regression models the adjusted hazard ratio for 5-year mortality of a CTO in a non-IRA was fairly similar when we used SVD as the reference or MVD without CTO as the reference category (2.2 and 2.6, respectively). These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.

CLINICAL IMPLICATIONS

An aggressive multivessel PCI strategy during and after primary PCI for STEMI has not improved outcome in MVD patients, both with and without DM. In fact, studies reported that treatment of non-culprit lesions in STEMI patients with MVD is associated with a higher post-procedural morbidity rate without a benefit in survival.[18-20] As in our previous reports, the findings of the present study suggest that additional revascularization strategies should perhaps be more focussed at treating total occlusions rather than stenoses in non-IRAs. Treating a CTO in a non-IRA during the primary procedure does not seem feasible, given the complexity of CTO angioplasty which requires a skilled and experienced operator and is associated with an increased use of contrast medium, and longer fluoroscopy time. A staged PCI procedure to revascularize a CTO in a non-IRA after STEMI seems to be a more sensible approach. We have therefore recently initiated the randomized controlled multicenter Evaluating XIENCE V and LVF in PCI on occLusiOns afteR STEMI (EXPLORE) trial to investigate the effects on left ventricular function and remodeling of opening a CTO in a non-IRA in a staged procedure within 1 week after primary PCI.[21]

Study Limitations

Several limitations of the current study should be mentioned. The study cohort is comprised of patients with a known diagnosis of DM at admission. We did not routinely measure haemoglobin A_{1c} or test for DM during admission. Furthermore, detailed information on peri- and post procedural medication (including glucose-regulating medication) was not available. Therefore we were not able to assess differences in glycemic control or adherence to guideline-based post-STEMI therapies. Moreover, we did not routinely store information on pre- or post-PCI renal function in our PCI database. Finally, some overestimation of non-culprit lesions may have occurred as non-culprit lesion stenosis severity was assessed in the acute setting on the infarct angiography by the performing cardiologist.[22]

CONCLUSION

Compared with patients with STEMI without DM, the prevalence of a CTO in a non-IRA is increased in STEMI patients with DM. In patients with DM, 5-year mortality was comparable between patients with SVD and patients with MVD without a CTO. The presence of a CTO in a non-IRA is a strong and independent predictor of 5-year mortality in diabetic STEMI patients treated with primary PCI. These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.

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Chapter 8

The Impact of Multivessel Disease With and Without a Coexisting Chronic Total Occlusion on Short and Long Term Mortality in ST-Elevation Myocardial Infarction Patients With and Without Cardiogenic Shock

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European Journal of Heart Failure 2013 Apr;15(4):425-32

ABSTRACT

Aims

To evaluate the impact of multivessel disease (MVD) with and without a chronic total occlusion (CTO) on early and late mortality in ST-elevation myocardial infarction (STEMI) patients with and without cardiogenic shock (CS).

Methods and Results

5018 STEMI patients were treated with primary percutaneous coronary intervention and stratified according to the presence of CS and the extent of coronary artery disease into single vessel disease (SVD), MVD without a CTO and MVD with a CTO. We performed a landmark mortality analysis up to 5-year follow-up with a landmark set at 30 days. In patients without CS (n=4409), only MVD with a CTO was an independent predictor for 30-day (HR:2.8,p<0.01) and 5-year mortality (HR:1.7,p<0.01), whereas MVD without a CTO was not associated with increased mortality. In CS patients (n=609), MVD with and without a CTO were independent predictors for 30-day mortality (HR:2.2,p<0.01, HR:1.8,<0.01). In 30-day CS survivors, only MVD with a CTO was associated with a trend towards increased mortality (HR:1.7,p=0.06).

Conclusion

In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, MVD with and without a CTO were predictors for short term mortality.

INTRODUCTION

Angiography in the setting of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) exposes the extent and severity of coronary artery disease. Around half of these patients suffer from multivessel disease (MVD). Patients with MVD have a worse prognosis compared to patients with single vessel disease (SVD).[1-3] The clinical management of these non-culprit lesions remains debatable as robust evidence on MVD management in the setting of primary PCI for STEMI is lacking.[4,5] Moreover, no clear beneficial effect has been shown in patients treated with multivessel PCI compared to culprit lesion PCI only. As a result, additional PCI for STEMI patients without cardiogenic shock (CS) is not recommended in the current ACC/AHA guidelines (class III).[6] For hemodynamically compromised patients, the guidelines state that if the stenotic artery perfuses a large area of myocardium and the procedure can be done efficiently, complete revascularization may improve long term prognosis.[7,8]

Recently our research group has shown that the prognostic value of MVD is almost completely driven by the presence of a chronic total occlusion (CTO) in a non-infarct related artery (IRA).[9] This novel concept has been confirmed in other STEMI datasets.[10-12] For patients presenting in CS, the impact of MVD with and without a coexisting CTO is less clear. In a subgroup of CS patients, we reported that MVD with a coexisting CTO was an independent predictor for 1-year cumulative mortality, while MVD without a CTO was borderline non significant.[13] These results were limited by a small sample size, especially with respect to CS patients.

In the present study, we sought to investigate an even longer follow-up time point and to assess the prognostic importance of MVD with or without a CTO in patients with STEMI according to the presence or absence of CS at time of index myocardial infarction. Prognosis was assessed with respect to left ventricular ejection fraction (LVEF) as well as crude mortality at follow-up. In order to distinguish early events, we performed a landmark mortality analysis at the 30 day time-point with a total follow-up period to 5 years.

METHODS

From January 1997 through December 2008, a total of 5307 consecutive and unselected STEMI patients treated with primary PCI in our hospital were entered in a dedicated database. Acute STEMI was diagnosed when patients had symptoms of an acute myocardial infarction lasting 30 minutes to 12 hours, accompanied by an electrocardiogram with ST-segment elevation >1 mm (0,1 mV) in ≥ 2 contiguous leads. Patients were immediately transported to the cardiac catheterization laboratory and underwent coro-

nary angiography with a view to perform primary PCI. PCI was performed by standard techniques, if the coronary anatomy was suitable. In our institution we only perform culprit lesion PCI, with only a rare exception for patients with CS.

Prior to PCI, all patients were treated with heparin (5000 IU) and aspirin (500 mg). Adjunctive treatment with glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Post PCI ticlopidine or clopidogrel was prescribed according to the guidelines.[14] Duplicate patients due to recurrent STEMI (n=192), patients with missing admission hemodynamic status (n=68) and patients lost to follow-up (n=29) were excluded, resulting in a final cohort of 5018 patients.

The final STEMI cohort was divided into patients with and without cardiogenic shock. Subsequently, all patients were stratified into three groups: patients with SVD, MVD without a CTO, and MVD with a coexisting CTO.

Data collection

Baseline characteristics, including demographic, clinical presentation and angiographic data, and hospital procedures were collected prospectively in the abovementioned dedicated database. Information on vital status was obtained from the Dutch national population registry (Statistics Netherlands, Voorburg, the Netherlands) per February 9, 2011. Patient data were checked for inconsistency and completeness. In case of conflicting or missing data outpatient files were reviewed and/or general practitioners were contacted by telephone.

Definitions

Multivessel disease was defined as at least 1 stenosis ≥70% in a non-infarct related epicardial artery or a stenosis ≥50% in the left main coronary artery. A CTO was defined as a 100% luminal narrowing in a non-IRA before PCI without antegrade flow or with antegrade or retrograde filling through collateral vessels. The degree of stenosis was determined by the operator by visual assessment of the diameter on angiography. Cardiogenic shock state was determined by the attending operator guided by a definition similar to the SHOCK trial, i.e. a systolic blood pressure persistently < 90 mm Hg or vasopressors required to maintain blood pressure >90 mm Hg, evidence of end organ hypoperfusion (e.g. urine output <30 ml or cold/diaphoretic extremities or altered mental status), and evidence of elevated filling pressures.[7] In addition shock was considered present when an intra-aortic balloon pump (IABP) or other circulatory support device was inserted for hemodynamic instability.

Left ventricular Function

LVEF was assessed by global visual estimation on echocardiography. Baseline LVEF was assessed within 10 days after the index event. The LVEF was dichotomized as either >40% or ≤40%.[15]

Primary Outcome

The primary outcome for the present analysis was all-cause 30-day and five-year mortality in 30-day survivors in patients with and without CS. The secondary outcome was LVEF after STEMI in patients with and without CS.

Statistical Analysis

Cumulative event-rates of all-cause death were estimated using the Kaplan-Meier method and compared using the Log Rank statistic. Follow-up for mortality was censored at the date of last follow-up by checking vital status in the Dutch population registry, or at five years, whichever came first. We performed a "landmark mortality analysis" with a landmark set at 30 days, in patients with and without cardiogenic shock. Hazard ratios for all-cause mortality were calculated using time extended Cox proportional hazard regression analyses after verification of the proportional hazards assumption. The multivariable model was built by stepwise backward variable selection with entry and exit criteria set at the p= 0.1 level. The following variables were included into the model: male gender, age (continuous), diabetes mellitus, hypertension, positive family history of cardiovascular disease, current smoking, hypercholesterolemia, previous myocardial infarction (MI), cardiogenic shock, left anterior descending (LAD) coronary artery-related MI, MVD without a CTO, MVD with a coexisting CTO, pre-procedural thrombolysis in myocardial infarction (TIMI) flow grade 3. Interaction terms between cardiogenic shock and the extent of the coronary artery disease with respect to the outcome variable all-cause mortality was tested by using the likelihood ratio statistic.

Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics and left ventricular function between the groups were tested for significance by the χ^2 test. Skewed-distributed continuous variables were compared with the Kruskal-Wallis test. Statistical significance was defined as a p-value <0.05.

RESULTS

Baseline Characteristics

Between January 1997 and December 2008, 5018 STEMI patients were treated with primary PCI. A total of 4409 (88%) STEMI patients presented without CS and 609 patients (12%) presented with CS. Of the total cohort, 3199 (64%) had SVD, 1153 (23%) had MVD

Table 1. Baseline Clinical, Angiographic and Procedural Characteristics.

	Total n=5018				Non Shock n=4409 (87.9%)				Shock n=609 (12.1%)			
	SVD n=3199	MVD n=1153	CTO n=666	P value	SVD n=2939	MVD n=978	CTO n=492	P value	SVD n=260	MVD n=175	CTO n=174	P value
Male (%)	70.5	74.2	74.5	0.02	71.1	74.3	74.6	<0.01	63.5	73.1	74.1	0.03
Age in years (median, IQR)	59 (50-69)	66 (56-75)	65 (56-75)	<0.01	58 (49-69)	66 (56-75)	64 (55-74)	<0.01	61 (52-71)	66 (56-75)	67 (60-76)	<0.01
Hypertension (%)	28.7	34.7	33.9	<0.01	29.0	36.9	37.6	<0.01	25.4	22.3	23.6	0.75
Smoker (%)	47.6	36.2	37.1	<0.01	48.8	37.2	39.0	<0.01	34.2	30.3	31.6	0.67
Hypercholesterolemia (%)	21.2	25.3	29.8	<0.01	22.0	25.8	31.7	<0.01	12.6	22.0	24.2	<0.01
Family history of CVD (%)	41.0	40.1	34.5	<0.01	42.6	42.3	38.2	0.19	23.1	27.4	24.1	0.58
Previous MI (%)	8.1	16.7	35.1	<0.01	8.0	16.5	33.7	<0.01	8.8	18.3	39.1	<0.01
Diabetes (%)	8.9	15.8	18.2	<0.01	9.0	15.7	17.3	<0.01	8.1	16.0	20.7	<0.01
Angiographic characteristics												
LAD related MI (%)	46.8	33.5	42.6	<0.01	45.7	32.4	40.9	<0.01	59.6	39.4	47.7	<0.01
Pre-Procedural TIMI flow grade 3 (%)	17.8	18.5	17.9	0.88	18.4	19.1	20.7	0.47	10.8	14.9	9.8	0.28
Post-Procedural TIMI flow grade 3 (%)	87.1	82.7	79.4	<0.01	88.3	85.2	83.3	<0.01	73.5	68.6	68.4	0.41
Procedural characteristics												
Thrombosuction (%)	33.7	29.1	23.1	<0.01	33.6	30.6	25.0	<0.01	34.6	21.1	17.8	<0.01
Glycoprotein IIb/IIIa inhibitor used (%)	26.5	25.8	29.3	0.25	25.5	24.0	25.8	0.64	38.5	36.0	39.1	0.82
Stent placement (%)	78.9	74.0	73.1	<0.01	78.8	74.1	74.2	<0.01	80.4	73.1	70.1	0.04

Abbreviations: CTO: chronic total occlusion, CVD: cardiovascular disease, IQR: inter-quartile range, MI: myocardial infarction, MVD: multivessel disease, LAD: left anterior descending coronary artery, MI: myocardial infarction, SVD: single vessel disease, TIMI: thrombolysis in myocardial infarction.

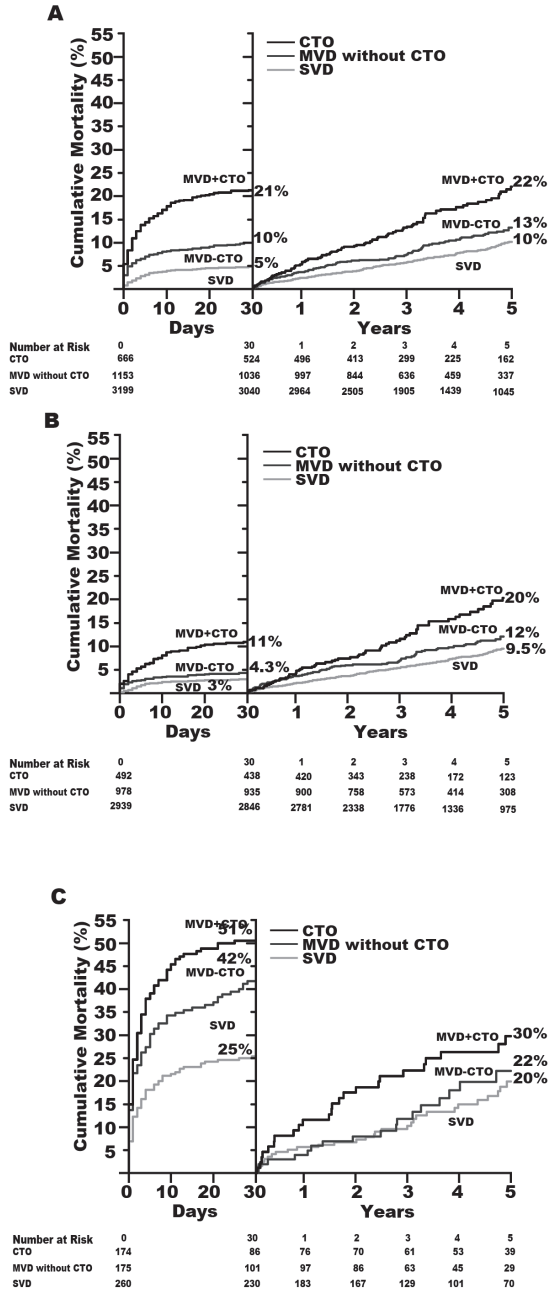

Figure 1. Landmark mortality analysis: risk of death during the first 30 days after primary PCI and thereafter in 30-day survivors for patients with SVD, MVD without a CTO or with a CTO. (A) The total cohort; (B) patients without shock; and (C) patients with shock.
CTO, chronic total occlusion; MVD, multivessel disease; PCI, percutaneous coronary intervention; SVD, single vessel disease.

without CTO and 666 (13%) had MVD with a coexisting CTO in a non-IRA. Of the non-CS STEMI patients, 2939 (67%) had SVD, 978 (22%) had MVD without CTO and 492 (11%) had MVD with a coexisting CTO in a non-IRA. Of the 609 patients with CS, 260 (43%) had SVD, 175 (29%) had MVD without a CTO; and 174 (29%) had MVD with a coexisting CTO in a non-IRA. Table 1 shows baseline clinical angiographic and procedural characteristics.

In the total cohort and non-CS cohort, patients with MVD (with and without a CTO) were older, had a higher prevalence of hypertension and diabetes, whereas they had a lower incidence of current smoking. The prevalence of hypercholesterolemia and a previous MI increased with the extent of coronary artery disease.

In the CS cohort, MVD patients with a coexisting CTO in a non-IRA were older and had a higher prevalence of hypercholesterolemia and diabetes. The prevalence of a previous MI increased with the extent of coronary artery disease. Patients with SVD more frequently suffered from a LAD-related MI.

Mortality in all patients

Median follow-up duration was 3.3 years (IQR:2.0-5.0 years). Figure 1A shows the Kaplan-Meier estimates for mortality for the three categories at 30 days and for the period thereafter until 5 years in 30-day survivors. At 30 days, the Kaplan-Meier estimates for mortality increased per extent of the coronary artery disease with the highest mortality in the MVD group with a coexisting CTO. In 30-day survivors, the Kaplan-Meier estimates for 5-year mortality were comparable between SVD and MVD without a CTO whereas the mortality in the group MVD with a CTO was approximately 2 times higher in comparison to the SVD group.

After multivariate adjustment MVD with and without a coexisting CTO in a non-IRA were predictors for 30-day mortality in comparison to SVD (HR:2.7,95% CI:2.1-3.4,p<0.01; event rates: 21.3% vs. 4.8% and HR:1.5,95% CI:1.1-1.9,p<0.01; event rates: 10% vs 4.8%, respectively; table 2). In 30-day survivors, MVD with a coexisting CTO was a significant predictor for 5-year mortality in comparison to SVD (HR:1.4,95% CI:1.1-1.8,p=0.02; event rates: 16.6% vs. 7.5%) in contrast to MVD without a CTO (HR:1.0,95% CI:0.8-1.3,p=0.93: event rates: 9.9% vs. 7.5%). There was a significant interaction between shock and multivessel disease with and without a CTO for mortality within 30 days but not for the period thereafter.

Mortality in patients without shock

Median follow-up duration was 3.5 years (IQR:2.1-5.0 years). The 30-day mortality and 5-year mortality in 30-day survivors in patients with MVD with a coexisting CTO was significantly higher in comparison to MVD patients without a CTO and SVD patients (figure 1B). In both time periods, the mortality between MVD without a CTO and SVD was comparable.

After multivariate adjustment, MVD with a coexisting CTO was associated with 30-day (HR:2.8,95% CI:1.9-4.0,p<0.01;event rates:11.0% vs. 3.0%) and 5-year mortality in 30-day survivors (HR:1.7,95% CI:1.2-2.3,p<0.01; event rates:14.4% vs. 6.9%) whereas MVD without a CTO was not a predictor for early (HR:1.0,95% CI:0.7-1.5,p=0.95; event rates: 4.3% vs 3.0%) or late mortality (HR:1.0,95% CI:0.8-1.3,p=0.98;event rates: 9.2% vs. 6.9%, respectively; table 2).

Table 2. Predictors of Mortality in STEMI patients treated with primary PCI.

	Unadjusted			Adjusted*		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Total Cohort (n=4658) Event rate= 15.3% (n=766)						
Time: 0-30 days						
MVD with CTO vs. SVD	4.8	3.8-6.1	<0.01	2.7	2.1-3.4	<0.01
MVD without CTO vs. SVD	2.1	1.7-2.7	<0.01	1.5	1.1-1.9	<0.01
Time: 30 days – 5 years						
MVD with CTO vs. SVD	2.3	1.8-3.0	<0.01	1.4	1.1-1.8	0.02
MVD without CTO vs. SVD	1.4	1.1-1.7	0.01	1.0	0.8-1.3	0.93
* adjusted for: age (continuous), hypercholesterolemia, left anterior descending coronary artery related myocardial infarction, positive family history of CVD, previous myocardial infarction and shock						
Non Shock Cohort (n=4092) Event rate= 11.1% (n=489)						
Time: 0-30 days						
MVD with CTO vs. SVD	3.8	2.7-5.3	<0.01	2.8	1.9-4.0	<0.01
MVD without CTO vs. SVD	1.4	1.0-2.1	0.05	1.0	0.7-1.5	0.95
Time: 30 days – 5 years						
MVD with CTO vs. SVD	2.2	1.7-3.0	<0.01	1.7	1.2-2.3	<0.01
MVD without CTO vs. SVD	1.4	1.1-1.7	0.02	1.0	0.8-1.3	0.98
* adjusted for: age (continous), diabetes mellitus, hypercholesterolemia, left anterior descending coronary artery related myocardial infarction, positive family history of CVD, previous myocardial infarction. and pre-procedural TIMI flow grade 3						
Shock Cohort (n=566) Event rate= 45.5% (n=277)						
Time: 0-30 days.						
MVD with CTO vs. SVD	2.3	1.7-3.2	<0.01	2.2	1.6-3.2	<0.01
MVD without CTO vs. SVD	1.8	1.3-2.5	<0.01	1.8	1.2-2.5	<0.01
Time: 30 days – 5 years						
MVD with CTO vs. SVD	1.8	1.3-3.0	0.04	1.7	1.0-3.0	0.06
MVD without CTO vs. SVD	1.1	0.6-2.1	0.66	1.1	0.6-2.0	0.83
* adjusted for: age (continous), hypertension, hypercholesterolemia, positive family history of CVD, smoking.						

Multivariable model was built by stepwise backward variable selection with entry and exit criteria set at the p= 0.1 level. All variables known before percutaneous coronary intervention were included in the initial analysis. Abbreviations: CTO: chronic total occlusion, CVD: cardiovascular disease, LAD: left anterior descending, MVD: multivessel disease, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction, SVD: single vessel disease and TIMI: thrombolysis in myocardial infarction.

Mortality in patients with shock

Median follow-up duration was 2.3 years (IQR:0-4.8 years). At 30 days, the Kaplan-Meier estimates for mortality increased per extent of the coronary artery disease with the highest mortality in the MVD group with a coexisting CTO (figure 1C). At 5 years, with exclusion of those who died in the first 30 days, Kaplan-Meier estimates of mortality between patients with SVD and MVD without a CTO were comparable throughout the entire follow-up period whereas the Kaplan-Meier estimates of mortality for the MVD group with a coexisting CTO was much higher. Figure 1C indicates a probably strong association with mortality at 3 years, which fades by 5 years as the number at risk drops.

MVD with and without a CTO were both significantly associated with 30-day mortality (HR:2.2,95% CI:1.6-3.2,p<0.01;event rates: 50.6% vs. 25.4% and HR:1.8,95% CI:1.2-2.5,p<0.01; event rates: 41.7% vs. 25.4%, respectively) however were not significantly associated with 5-year mortality in 30-day survivors (HR:1.7,95% CI:1.0-3.0,p=0.06; event rates: 27.9% vs. 15.5% and HR:1.1,95% CI:0.6-2.0,p=0.83; event rates: 16.7% vs 15.5%, respectively; table 2).

Left ventricular function

Of the 5018 STEMI patients, echocardiography within 10 days was present in 32%, nonCS cohort: n=1428 with a median time to echo of 3 days (IQR: 2-4) and CS-cohort: n=177 with a median time to echo of 3 days (IQR: 1-6). The proportion of non CS patients with a LVEF ≤ 40% was 15% for SVD, 14% for MVD without a CTO and 23% for MVD with a CTO, figure 2A. The proportion of CS patients with a LVEF ≤ 40% was 24% for SVD, 44% for MVD without a CTO and 42% for MVD with a CTO, figure 2B. In patients without CS, MVD with a coexisting CTO was more often associated with LVEF ≤ 40% in comparison to patients with MVD without a CTO or SVD whereas in patients with CS, MVD with and without a CTO were both more often associated with LVEF ≤ 40% in comparison to patients with SVD, figure 2A and B).

To investigate whether the long inclusion period could potentially introduce bias to our results due to changes in both medical and interventional therapies, we divided the cohort into two time periods: 1997-2002 and 2003-2008. The hazard ratios seen in these two time periods were comparable for the total and the non-CS cohort, except for late mortality in the CS cohort where the presence of MVD with a coexisting CTO seems to have a larger effect on mortality between 2003-2008 in comparison to 1997-2002. However, the event rate for late mortality in 30-day survivors is too low to explore a reliable association. In each cohort, time was not a significant confounder as the addition of time to the multivariate model had no important influence on the hazard ratios of MVD with and without a CTO.

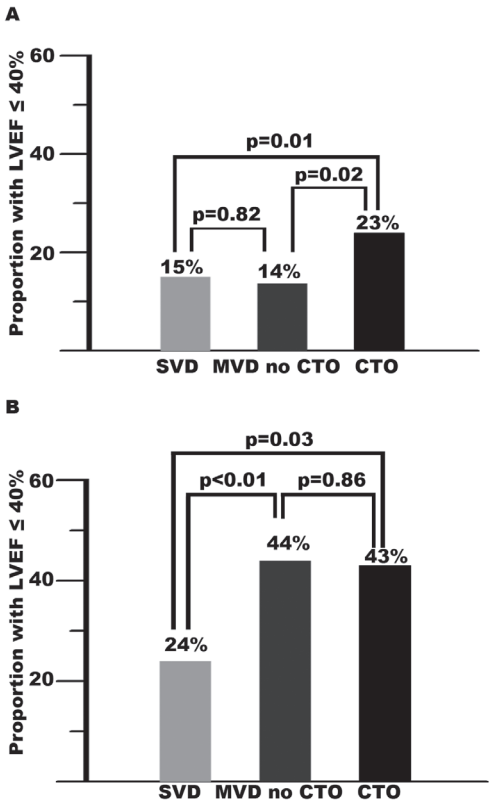

Figure 2. Proportion of patients with a LVEF ≤ 40% after STEMI.
Echocardiography within 10 days after the index event was present in 1605 patients. (A) The number of non-CS patients with an LVEF ≤40% was 142 for SVD, 44 for MVD without a CTO, and 33 for MVD with a CTO. (B) The number of CS patients with an LVEF ≤40% was 22 for SVD, 20 for MVD without a CTO, and 17 for MVD with a CTO. CS, cardiogenic shock; CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; MVD, multivessel disease; STEMI, ST-elevation myocardial infarction; SVD, single vessel disease.

DISCUSSION

The present analyses show that in STEMI patients without cardiogenic shock, MVD is only associated with short- and long-term mortality when a coexisting CTO is present. In these non-shock patients, only MVD with a coexisting CTO was associated with a reduced LVEF after STEMI in comparison to MVD without a CTO and SVD.

In patients with cardiogenic shock, MVD with and without a coexisting CTO were both associated with 30-day mortality. However, both variables lost its predictive value in 30-day survivors up to 5 years of follow-up in comparison to SVD, although for MVD with a CTO, the association was only borderline non-significant. Finally, in the shock

cohort, MVD with and without a coexisting CTO were associated with a reduced LVEF after STEMI in comparison to SVD patients which is different from patients without CS.

This analysis is of additional value to our previous reports, in a smaller STEMI patient cohort, concerning the impact of MVD with and without a CTO.[9,13] Our previous studies led us to the hypothesis that MVD with and without a CTO might have a different impact on short and long term mortality when stratified by hemodynamic instability. It is likely that the important increase of our study cohort has better revealed the impact of MVD with and without a CTO in CS STEMI patients, as in the present analysis MVD with and without a coexisting CTO are both important predictors for short term mortality. However, in 30-day survivors, MVD without a CTO lost its predictive value on long-term mortality. After multivariate analysis, the presence of a CTO showed a trend towards increased late mortality. Due to the high 30-day mortality rate (50%), a filtering effect potentially reduces power to detect a significant difference for late mortality.

The impact of MVD with a concurrent CTO in STEMI patients have been confirmed in several other registries and sub-analysis of randomized trials.[9,10,12,16] Besides our research group, only one paper performed a landmark analysis with a landmark set on 30 days.[12] The presence of a CTO was an independent predictor for early and late mortality, whereas MVD without a CTO was borderline significant for early mortality with a p-value of 0.0495. In this trial cardiogenic shock was not an exclusion criterion however the percentage of included CS patients was low, possibly explaining the borderline effect of MVD without a CTO in the total cohort. To our knowledge, the current paper is the first to report on the effect in CS and non-CS STEMI patients. The impact of MVD with and without a coexisting CTO on early and late mortality could be due to reduced LVEF after STEMI. In patients without CS, the LVEF was significantly lower in the MVD group with a coexisting CTO in comparison to the MVD without a CTO and the SVD group. When a CTO is present, the underlying myocardium is perfused through collateral circulation which can be endangered when the donor artery is blocked in case of STEMI. The area at risk would then be much larger resulting in an extent of final infarct size.

In patients with CS, MVD with and without a CTO were associated with reduced LVEF compared with SVD. CS patients have reduced cardiac output and coronary blood flow which may increase the functional importance of non-occlusive MVD lesions, resulting in myocardial ischemia in other perfusion areas than that of the culprit lesion. Interestingly, in non-CS patients only MVD with a coexisting CTO was associated with reduced LVEF.

The current study identified the presence of a CTO as a unique marker for worse short term prognosis in non-shock patients and identified MVD with and without a CTO as markers for worse short term prognosis in shock patients. These markers may be a target for additional revascularisation in the sub-acute STEMI phase. Current ACC/AHA guidelines on primary PCI for STEMI state that in hemodynamic stable STEMI patients

only culprit lesion PCI should be performed and that PCI of non-infarct lesions is not recommended (class III, level of evidence C). This recommendation was recently confirmed by several meta-analyses.[4,5] However, revascularization of non-culprit lesions could be beneficial in patients who are hemodynamically compromised.[6] The recommendation for additional revascularization in CS patients is derived from the SHOCK trial that aimed for complete revascularization.[7] Our data show that MVD with and without a CTO are both predictors for mortality in CS patients. As mentioned, additional PCI for MVD in non-CS patients is not recommended and in our report its impact is clearly driven by the presence of a CTO. However, large randomized controlled trials are needed to evaluate the possible beneficial effect of CTO revascularisation in STEMI patients without CS and complete revascularisation in STEMI patients with CS. Therefore we initiated a global multicenter randomized controlled trial in non-CS STEMI patients, to investigate a possible beneficial effect of opening a CTO in a non-IRA in a staged PCI procedure within one week after STEMI on LVEF and left ventricular dimensions: the EXPLORE (Evaluating XIENCE V and LVF in PCI on Occlusions after STEMI) trial.[17]. CTO revascularization during the primary procedure is not feasible as its success depends largely on the operator's skills, lengthens the procedure considerably with also increased use of contrast media and fluoroscopy time. Therefore, we scheduled the procedure in the semi-acute phase.

In the elective setting, only observational data is available comparing successful versus unsuccessful PCI of CTO. Successful PCI of CTO is associated with improved quality of life, LVF and survival.[18-21] Another suggested theoretical benefit of CTO revascularization in the elective setting is the protective effect during future events by providing collateral circulation to the IRA. The EXPLORE trial will also address this hypothesis.[17]

Limitations

Several limitations of the present study should be mentioned. The study concerns a single center study, reflecting local skills and practice. Therefore the results cannot be extrapolated to other centers. Nevertheless, several other studies have observed the same impact of CTO in STEMI patients in general. Non-culprit lesion stenosis severity was assessed at the infarct angiography in the acute setting and by the performing cardiologist. Therefore, some overestimation of non-culprit lesions might have occurred.[22] Furthermore, detailed information about the medical treatment and revascularisation of non-culprit lesions during the follow-up period was not available. Also, during this time period, no information was available on kidney function or history of heart failure and therefore could not be corrected for during multivariate adjustment. In addition, the LVEF was not routinely assessed during admission and therefore information about LVEF was not available in all patients. Information about time of symptom onset to treatment was not available in all patients and could therefore not be included in the analyses.

However, no differences were observed in that proportion of the patients for which time to treatment data were available.

CONCLUSION

In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, MVD with and without a CTO were predictors for short term mortality.

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Chapter 9

The Impact of the Location of a Chronic Total Occlusion in a Non-Infarct Related Artery on Long-term Mortality in ST-Elevation Myocardial Infarction Patients

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EuroIntervention, accepted

ABSTRACT

Aims

Several studies evaluated the impact of a CTO on short- and long term mortality in STEMI patients. It has been speculated that the adverse effect on prognosis could differ per coronary location.

Methods and Results

Between 2000 and 2012, a total of 480 STEMI patients with a CTO in a non-infarct related artery were included. The primary outcome for the present analysis was all-cause three-year mortality, evaluating the impact of the coronary CTO and infarct location. 413 had a single CTO in a non-infarct related artery whereas 67 patients had more than 1 CTO in whom mortality was higher. In patients with a single CTO, the highest risk of mortality was observed when the culprit lesion was located in the LAD or proximal LCX or when the CTO lesion was located in the proximal LAD.

Conclusions

We previously reported that STEMI patients with a CTO have a worse prognosis than STEMI patients without a CTO. We now show that in these patients, LAD or proximal LCX location for the culprit lesion or proximal LAD location for the CTO lesion were associated with the highest risk. As a result almost all CTO patients are at increased risk for mortality due to the combination of the culprit and CTO artery location.

INTRODUCTION

Increased angiographic severity and extent of coronary artery disease is associated with higher mortality [1-4]. Coronary chronic total occlusions (CTO) are often considered the most complex expression of coronary artery disease. In patients with significant coronary artery disease a chronic total occlusion (CTO) is present in approximately 16%.[5,6] Previously, several studies in patients with stable coronary artery disease reported that successful versus failed elective CTO revascularization has been associated with symptom relief [7], reduced need for coronary artery bypass surgery[8], improvement of electrical stability[9,10] and left ventricular function and even reduced mortality. A recent meta-analysis reported an increment of 4.44% in left ventricular ejection fraction and reduced of long-term mortality after successful versus failed CTO revascularization (OR: 0.52).[11] However, it has been postulated that these beneficial effects might vary according to the anatomical location of the CTO, showing only an improved survival after treatment of the left anterior descending coronary artery (LAD) and left circumflex (LCX) but not the right coronary artery (RCA)[12,13]. Several studies have shown a strong association between the presence of a concurrent CTO in ST-elevation myocardial infarction (STEMI) patients and short- and long term mortality.[14-17] The purpose of this study is to evaluate if long term prognosis of STEMI patients differ according to the coronary location of the CTO.

METHODS

Study cohort

From January 2000 through December 2012, STEMI patients with a CTO in a non-infarct related artery (IRA) treated with primary percutaneous coronary intervention (PCI) in our hospital of whom the diagnostic angiography was available, were entered in a dedicated database after informed consent and approval by our institutional review committee. Acute STEMI was diagnosed when patients had symptoms of an acute myocardial infarction lasting 30 minutes to 12 hours, accompanied by an electrocardiogram with ST-segment elevation >1 mm (0,1 mV) in ≥ 2 contiguous leads. Patients were immediately transported to the cardiac catheterization laboratory and underwent coronary angiography with a view to perform primary PCI. PCI was performed by standard techniques, if the coronary anatomy was suitable.

Prior to PCI, all patients were treated with heparin (5000 IU) and aspirin (500 mg). Adjunctive treatment with glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Post PCI antiplatelet therapy was prescribed according to the guidelines, clopidogrel, prasugrel or ticagrelor. Duplicate patients due to recurrent STEMI or patients lost to

follow-up were excluded. Patients with a previous CABG surgery were excluded due to the complexity of inter-arterial connections and patency of the graft and native vessel.

Data collection

Baseline characteristics were collected prospectively in the aforementioned dedicated database. Information on vital status was obtained from the Dutch national population registry (Statistics Netherlands, Voorburg, the Netherlands). Patient data were checked for inconsistency and completeness.

Angiographic analysis

All coronary angiograms were reviewed by an experienced CTO operator (JH) and a fellow (LH).

Definitions

A CTO was defined as a 100% luminal narrowing in a non-IRA before PCI without antegrade flow or with antegrade or retrograde filling through collateral vessels.

Proximal lesions were considered segment 6 or 7 for the LAD coronary artery and segment 11 for the LCX coronary artery.

Primary Outcome

The primary outcome for the present analysis was all-cause three-year mortality in STEMI patients with a CTO, evaluating the impact of the coronary CTO location corrected for the culprit artery with the exclusion of left main lesions and multiple CTO patients due to its low prevalence.

Statistical analysis

Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics between the groups were tested for significance by the χ^2 test. Statistical significance was defined as a p-value <0.05. Cumulative event-rates of all-cause death were estimated using the Kaplan-Meier method and compared using the Log Rank statistic. Follow-up for mortality was censored at the date of last follow-up by checking vital status in the Dutch population registry, or at 3 years, whichever came first. Hazard ratios for all-cause mortality were calculated using Cox proportional hazard regression analyses after verification of the proportional hazards assumption. The multivariable model was built by adding covariates from the baseline characteristics table with a p-value <0.10 in univariate analysis. All variables with a p-value >0.10 were removed from the model.

RESULTS

Between 2000 and 2012, 6771 unique STEMI patients underwent primary PCI of which 744 (11%) had a CTO (figure 1). In 172 (23%) CTO patients the coronary angiogram was irretrievable and in 7 (1%) patients the quality of the angiogram was insufficient for analysis. Of the remaining patients, 72 (10%) were excluded due to previous CABG and 13 (2%) patients did not receive primary PCI, resulting in a CTO cohort of 480 patients.

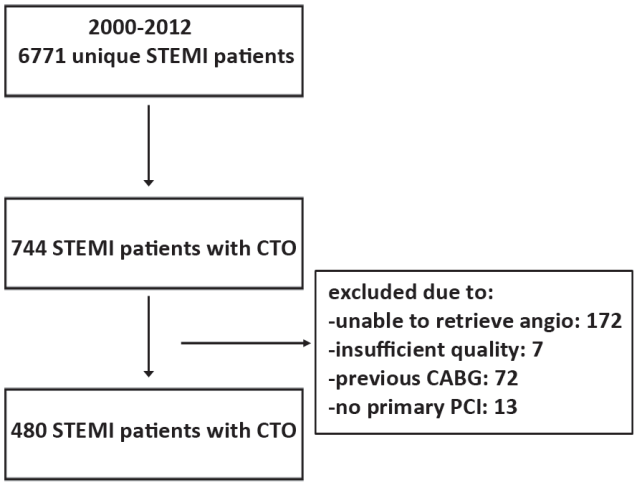


Figure 1. Flowchart. Abbreviations: CABG: coronary artery bypass graft surgery, CTO: chronic total occlusion, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction.

Patient characteristics

Of these patients, 413 had a single CTO in a non-infarct related artery whereas 67 patients had more than 1 CTO, see table 1. The majority of the CTO patients were male (76%) with a mean age of 64 years (55-74). Approximately a quarter of the patients had a previous MI and a similar proportion of patients was in cardiogenic shock upon presentation. The culprit lesion was in the LAD in 44% of cases, in the RCA in 32% of patients, in the LCX in 23% of patients, and in the left main in 1%. The latter group was excluded from the primary analysis due to its low prevalence. The culprit lesion was most often treated with stent placement (90%) with a post-procedural thrombolysis in myocardial infarction flow grade 3 in 85%. Among patients with a single CTO in a non-IRA, the CTO was most often located in the RCA (47%) and less often in the LCX (30%) and LAD (23%). There were no significant differences regarding the baseline characteristics between these groups.

Table 1. Baseline characteristics of STEMI patients with a CTO, overall and stratified for the coronary location.

	All patients (n=480)	Single CTO RCA (n=196)	Single CTO LAD (n=93)	Single CTO LCX (n=124)	P-value*	Multiple CTO (n=67)
Male gender (%)	75.8	75.5	74.2	72.6	0.84	85.1
Age (median, IQR)	64.3 (55-74)	63.5 (53.3-72.8)	65 (54-76)	66 (56-73.8)	0.22	65.8 (53-68.7)
Diabetes (%)	16.0	19.5	11.2	16.4	0.23	15.2
Hypertension (%)	3.8	36.3	32.6	38.5	0.67	33.3
Hyperlipidemia (%)	32.5	34.0	25.0	36.7	0.19	30.3
Current smoker (%)	44.3	46.2	40.2	41.0	0.54	49.3
Previous MI (%)	25.4	22.1	33.3	24.6	0.13	25.8
Cardiogenic shock(%)	25.8	26.5	17.2	25	0.21	37.3
Coronary Anatomy					<0.01	
Right dominance (%)	88.3	85.6	92.5	89.5		89.6
Left dominance (%)	4.8	2.1	4.3	8.9		6.0
Balanced (%)	6.7	12.3	3.2	1.6		4.5
Multiple CTOs (%)	14	-	-	-	-	100
Three Vessel disease	54.8	46.1	48.4	55.6	0.25	100
Culprit Lesion (%)					<0.01	
RCA (%)	32.1	-	72	58.9		20.9
LCX (%)	23.1	36.7	28	-		19.4
LAD (%)	43.8	61.7	-	40.3		58.2
LM (%)	1	1.5	-	0.8		1.5
Stent placement (%)	90.4	88.2	92.5	93.5	0.22	89.6
DES use (%)	18.4	19.6	11.8	21.0	0.18	19.7
TIMI 3 flow pre-PPCI (%)	19.4	16.3	24.7	17.7	0.22	23.9
TIMI 3 flow post-PPCI (%)	85	81.6	87.1	85.5	0.43	91.0
Mortality at 3 years	25.8	28.1	22.6	21.8	0.36	31.3

Abbreviation: CTO= chronic total occlusion, IQR= inter quartile range, LAD= left anterior descending artery, LCX= left circumflex coronary artery, LM=left main coronary artery, RCA=right coronary artery, STEMI= ST-elevation myocardial infarction, TIMI= thrombolysis in myocardial infarction. PPCI=primary percutaneous coronary intervention. *p-value over the single CTO group.

Figure 2 shows three-year mortality of the STEMI cohort stratified according to single versus multiple CTO. Long-term mortality was higher in the latter group. As these patients have an increased risk compared to single CTO patients, they were therefore excluded from the primary analysis.

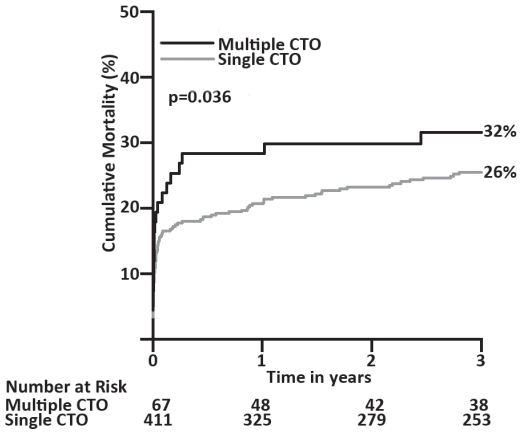
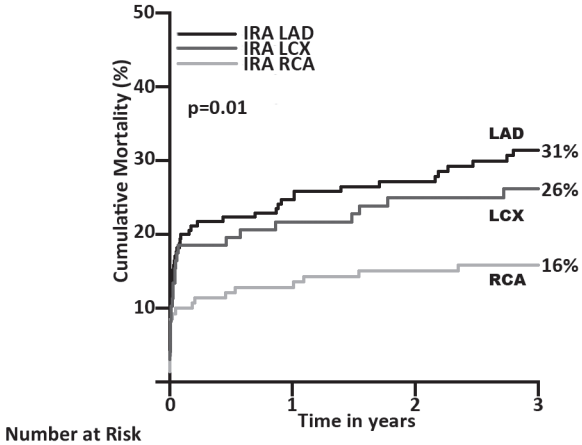


Figure 2. Mortality in STEMI patients with a single versus multiple CTO.
Abbreviations: CTO: chronic total occlusion, STEMI: ST-segment elevation myocardial infarction.

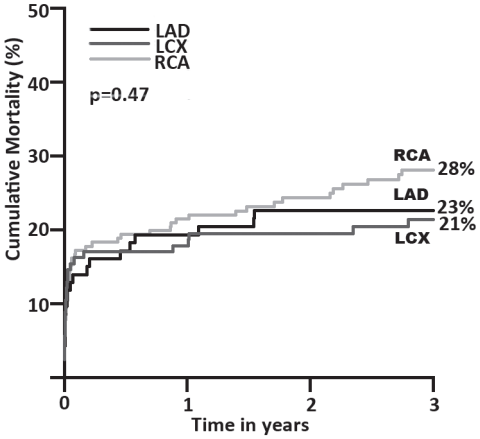
Prognostic impact according to coronary location

Figure 3 shows long-term mortality according to the location of the culprit artery and figure 4 shows mortality after stratification of the cohort according to the CTO artery. In this cohort the mortality of STEMI patients with a CTO and the culprit artery in the LAD (31%) or LCX (26%) was comparable while mortality in the RCA group was lower (16%). When the cohort was stratified according to location of the CTO (figure 4), the highest mortality was observed in STEMI patients with a CTO located in the RCA (28%), and the lowest mortality in patients with the CTO in the LAD (23%) or LCX (21%). When corrected for the location of the culprit artery and other significant variables, a CTO located in the LAD was associated with a non-significant increased risk for mortality compared to a CTO located in the RCA or LCX (HR: 1.6 95% CI: 0.8-3.1,p=0.15, HR 1.2 95% CI 0.7-2.0, p=0.60) (table 2). When the left coronary system was stratified into a proximal and distal part, a CTO located in the proximal LAD was associated with significantly increased mortality compared with a CTO located in the RCA (HR:2.2, 95% CI: 1.1-4.5, p=0.02), table2. For the culprit lesion, a location in the LAD or proximal LCX was associated with a worse survival compared to the RCA, table 2. As a result, when the CTO is located in the RCA, the culprit artery must be situated in the LAD or LCX and thus, through the combination of CTO and the culprit location, the majority of the cohort was at a high risk for mortality which is shown in table 4. Patients with the culprit artery in the RCA and a concurrent CTO in the LAD or LCX had the lowest absolute 3 year mortality rate. In all other combinations, the mortality rate was at least twice as high with the highest mortality rate in patients with a culprit artery located in the LCX and the CTO artery located in the LAD. When cardiogenic shock was included in the model, only age remained a significant predictor for mortality (table 3).



Number at Risk				
LAD	170	128	106	94
LCX	97	75	66	61
RCA	140	122	107	98

Figure 3. Mortality in STEMI patients with a single CTO stratified according to culprit related artery. Abbreviations: CTO: chronic total occlusion, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, STEMI: ST-segment elevation myocardial infarction.



Number at Risk				
LAD	93	75	66	61
LCX	123	101	89	80
RCA	191	145	124	112

Figure 4. Mortality in STEMI patients with a single CTO stratified according to CTO related artery. Abbreviations: CTO: chronic total occlusion, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, STEMI: ST-segment elevation myocardial infarction.

Table 2. The predictive value of coronary lesion location, including proximal or distal location, for long term mortality (cardiogenic shock not included in the model).

	HR	95% CI	p-value	HR	95% CI	p-value
	Univariate analysis			Multivariate correction		
Infarct related artery						
RCA	-	-	-	-		
LAD	2.1	1.3-3.5	0.02	2.7	1.4-5.2	<0.01
LCX	1.7	1.0-3.1	0.06	2.3	1.2-4.5	0.01
CTO related artery						
RCA	-	-	-	-		
LAD	0.8	0.5-1.3	0.49	1.6	0.8-3.1	0.15
LCX	0.8	0.5-1.2	0.48	1.2	0.7-2.0	0.60
Proximal/Distal lesion location						
Infarct related artery						
RCA	-	-	-	-		
LAD proximal	2.0	1.2-3.4	<0.01	2.6	1.3-5.0	<0.01
LAD distal	2.6	1.3-5.4	<0.01	2.9	1.1-7.2	0.02
LCX proximal	1.9	0.9-3.8	0.08	2.4	1.1-5.6	0.04
LCX distal	1.6	0.8-3.2	0.18	1.9	0.9-3.9	0.10
CTO related artery						
RCA	-	-	-	-		
LAD proximal	1.2	0.7-2.0	0.51	2.2	1.1-4.5	0.02
LAD distal	0.2	0.05-0.8	0.03	0.5	0.1-2.1	0.32
LCX proximal	0.6	0.3-1.4	0.25	0.7	0.3-1.8	0.48
LCX distal	0.8	0.5-1.4	0.48	1.4	0.8-2.5	0.28

Multivariate analysis: corrected for age, gender and statin use.

Abbreviation: CI= confidence interval, CTO= chronic total occlusion, HR= hazard ratio, LAD= left anterior descending artery, LCX= left circumflex coronary artery, RCA=right coronary artery, STEMI= ST-elevation myocardial infarction.

Table 3. The predictive value of coronary lesion location, including proximal or distal location, for long term mortality (cardiogenic shock included in the model).

	HR	95% CI	p-value	HR	95% CI	p-value
	Univariate analysis			Multivariate correction		
Infarct related artery						
RCA	-	-	-	-		
LAD	2.1	1.3-3.5	0.02	1.2	0.6-2.4	0.59
LCX	1.7	1.0-3.1	0.06	1.2	0.6-2.3	0.69
CTO related artery						
RCA	-	-	-	-		
LAD	0.8	0.5-1.3	0.49	1.2	0.6-2.3	0.60
LCX	0.8	0.5-1.2	0.48	0.9	0.5-1.5	0.57
Proximal/Distal lesion location						
Infarct related artery						
RCA	-	-	-	-		
LAD proximal	2.0	1.2-3.4	<0.01	1.1	0.6-2.3	0.72
LAD distal	2.6	1.3-5.4	<0.01	1.1	0.4-2.9	0.83
LCX proximal	1.9	0.9-3.8	0.08	1.0	0.4-2.4	0.96
LCX distal	1.6	0.8-3.2	0.18	1.2	0.6-2.5	0.68
CTO related artery						
RCA	-	-	-	-		
LAD proximal	1.2	0.7-2.0	0.51	1.4	0.7-2.9	0.33
LAD distal	0.2	0.05-0.8	0.03	0.4	0.1-1.6	0.19
LCX proximal	0.6	0.3-1.4	0.25	0.6	0.2-1.4	0.20
LCX distal	0.8	0.5-1.4	0.48	1.0	0.5-1.8	0.94

Multivariate analysis: corrected for age, gender, statin use and cardiogenic shock.
Abbreviation: CI= confidence interval, CTO= chronic total occlusion, HR= hazard ratio, LAD= left anterior descending artery, LCX= left circumflex coronary artery, RCA=right coronary artery, STEMI= ST-elevation myocardial infarction.

Table 4. Three-year absolute mortality in STEMI patients with a single CTO in a non-IRA.

	IRA-RCA	IRA-LAD	IRA-LCX
CTO-RCA	-	30.6%	20.8%
CTO-LAD	16.4%	-	38.5%
CTO-LCX	15.1%	30.0%	-

DISCUSSION

Previous literature showed increased mortality in STEMI patients with versus without a CTO in a non-infarct related artery. In this paper, we showed that within these patients the highest mortality was observed when a CTO was located in the proximal LAD or the culprit artery in the LAD or proximal LCX. Until now, no literature exists where mortality is evaluated in STEMI patients with a CTO in a non-IRA according to the coronary location of the CTO and the culprit artery although the importance of the LAD seems intuitive as reduced mortality might be explained by the prognostic significance of left ventricular function. As left ventricular function is related to cardiogenic shock, it could explain our finding that all prognostic significance of CTO or culprit location was lost after adding cardiogenic shock in the multivariate model. The importance of the anterior wall of the left ventricle on prognosis, which is for the larger part dependent on the LAD for blood supply, has been well documented in both stable coronary artery disease as in patients with myocardial infarction[18-20]. Compared with a myocardial infarction not related to the LAD, or distal versus proximal LAD-related myocardial infarction, those patients have a worse clinical outcome in terms of mortality, hemodynamic instability, need for left ventricular assist devices which is probably due to lower residual left ventricular ejection fraction (LVEF), caused by a larger final infarct size.[19,21-26] In addition, the observed lower myocardial blush grade in proximal LAD culprit lesions could be related to a larger infarct size, more edema, higher filling pressures, and increased downstream microvascular resistance.[27] Comparable findings have been observed in STEMI patients with a CTO in whom mortality, residual left ventricular function, hemodynamic stability, ST-segment resolution and MBG were worse compared to non-CTO STEMI patients[15-17,27,28], however these endpoints have never been specified according to coronary location.

Another explanatory mechanism could be an alteration in the balance of the autonomic nervous system owing to the location of coronary occlusion which has been associated with life threatening ventricular arrhythmias and cardiac death in survivors of myocardial infarction.[29] Sympathetic innervation is less pronounced in the inferior compared with the anterior myocardial wall whereas vagal afferent receptors have a preferential distribution on the posterior wall of the left ventricle.[30,31] In animal experiments, vagal stimulation or sympathetic inhibition reduces the threshold for ventricular fibrillation.[32] Therefore, patients with an acute inferior occlusion after myocardial infarction might be relatively protected from ventricular fibrillation in contrast to patients with an acute anterior occlusion who might have a higher frequency of ventricular arrhythmia. In a small cohort ($n = 23$), CTO PCI has proven to have a beneficial effect on the autonomic nervous system in the LAD artery, which was not observed after CTO PCI of the RCA.[33] These findings suggest a potential antiarrhythmic effect after LAD revascularization, resulting from a shift in the autonomic balance in favor of the parasympathetic nervous system.

Our cohort presents a group with high mortality rates, depending on the combination of coronary location between 15.1% and 38.5%. In a large cohort of STEMI patients treated with primary PCI the 5-years mortality rates for SVD, MVD without CTO and MVD with CTO were, 14%, 20% and 38% respectively[5,6]. Our data emphasise the need for further assessment of the optimal treatment strategy in these challenging patients.

Currently, no randomized data exist whether revascularization of a CTO in STEMI or stable angina patients can actually reverse the observed worse outcome. Currently, three randomized trials are enrolling patients, one in STEMI patients, the EXPLORE trial[34] which will evaluate whether CTO–PCI in a non-infarct-related artery within 7 days of primary PCI can improve LVEF and reduce left ventricular end-diastolic volume at 4 months follow-up, compared with optimal medical therapy in 300 STEMI patients. The other two randomized clinical trials are currently enrolling patients with CTO and stable coronary artery disease, namely the EuroCTO trial[35] which will randomly assign 1,200 patients to receive either PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is quality of life at 1 year and major cardiovascular events at 3 years. Similarly, the DECISION-CTO trial[36] will randomly assign 1,284 patients to receive PCI with DES and optimal medical therapy or optimal medical therapy alone. The primary end point is a composite of all-cause mortality, myocardial infarction, stroke, and any revascularization at 3-year follow-up. Although randomized data is lacking, observational studies have shown several beneficial effects after CTO revascularization in patients with stable angina such as improvement in angina and quality of life,[7] a potential improvement in electrical myocardial stability[9,10] a reduced need for CABG surgery,[8] enhanced tolerance of future coronary events, increased left ventricular function, and a substantial increase in survival.(11) Two observational studies evaluated the difference in survival after CTO revascularization in patients with stable CAD according to the target vessel and found only a survival benefit after successful CTO PCI in either the LAD or the LCX arteries, but not in the RCA.[12,13] As mentioned above, survival data in STEMI patients after CTO revascularization is absent.

Several limitations are applicable to this study. Importantly, our study is limited by its observational nature and its modest cohort size. Due to the unbalanced known IRA distribution in a general STEMI population with the LCX being the least frequent IRA and the RCA being the most frequent CTO artery, there is an overall unbalanced distribution of combinations of (CTO/IRA) arteries. Although is in accordance with daily clinical practice, this may be a limitation upon interpreting the presented results.[12,13] Furthermore, although multivariate Cox proportional hazards models were constructed, unknown or unmeasured confounders may still introduce bias. No complete data was available on possible mechanisms explaining the observed difference in mortality by target vessel, such as infarct size and left ventricular function. More research is needed to elucidate

these mechanisms. Last, the coronary angiograms not analysed by an independent core lab.

In conclusion, we previously reported that STEMI patients with a CTO have a worse prognosis than STEMI patients without a CTO. We now show that in these patients, LAD or proximal LCX location for the culprit lesion or proximal LAD location for the CTO lesion were associated with the highest risk. As a result almost all CTO patients are at increased risk for mortality due to the combination of the culprit and CTO artery location.

CLINICAL PERSPECTIVES

Increased angiographic severity and extent of coronary artery disease is associated with higher mortality. In patients with significant coronary artery disease a chronic total occlusion (CTO) is present in approximately 16%. Several studies have shown a strong association between the presence of a concurrent CTO in ST-elevation myocardial infarction (STEMI) patients and short- and long term mortality. The purpose of this study is to evaluate if long term prognosis of STEMI patients differ according to the coronary location of the CTO. This report shows that the highest risk of mortality was observed when the culprit lesion was located in the LAD or proximal LCX or when the CTO lesion was located in the proximal LAD. In clinical practice, these patients constitute a very high risk group. Whether CTO intervention in addition to primary PCI could improve prognosis will be answered shortly in the the EXPLORE trial.

Impact on daily practice

Whether CTO intervention in addition to primary PCI could improve prognosis will be answered shortly in the the EXPLORE trial. The patients who would theoretically benefit the most regarding mortality is when the culprit lesion was located in the LAD or proximal LCX or when the CTO lesion was located in the proximal LAD.

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Chapter 10

Alles dotteren bij het hartinfarct? Voorlopig niet

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Nederlands Tijdschrift voor Geneeskunde 2014;158.

SAMENVATTING

Onlangs werd een trial stopgezet omdat al snel bleek dat preventief dotteren van alle vernauwde kransvaten bij een hartinfarct – en niet alleen het 'schuldige' vat oprekken – gunstig is. Maar klopt die uitkomst wel? Hoebers en Henriques zetten hun vraagtekens bij de studieopzet.

Behandeling voor een acuut myocardinfarct houdt in dat het aangedane, 'schuldige' vat (de 'culprit') meteen gedotterd wordt. Bij ongeveer de helft van deze patiënten zijn er daarnaast ook andere vernauwingen, die geen relatie hebben met het acute hartinfarct. Patiënten met meervatslijden hebben een slechtere prognose dan patiënten met eenvatslijden van de kransslagaders. Uit meerdere retrospectieve studies blijkt dat aanvullend dotteren van andere vaten in de acute fase mogelijk samenhangt met een toename van hartinfarcten en een slechtere prognose. Aanvullende revascularisatie wordt daarom pas later verricht, afhankelijk van klachten en diagnostiek naar ischemie. Electieve dotterbehandelingen kunnen wel de klachten verhelpen echter lijkt het geen effect te hebben op de prognose. De uitkomst van de PRAMI-studie is dus opmerkelijk. Voor het eerst suggereren onderzoekers dat dotteren van alle vernauwingen in de acute fase wél tot een betere prognose leidt. Dit lijkt onrealistisch. In onze opinie is een studie opzet met een samengesteld eindpunt waarin de normale behandelingsstrategie is opgenomen een methode om een positieve uitkomstmaat te krijgen echter zonder klinische relevantie.

INTRODUCTIE

Afgelopen september publiceerde het *New England Journal of Medicine* de uitkomsten van de PRAMI-studie, een gerandomiseerde studie onder 465 patiënten die een acuut hartinfarct hadden en daarnaast vernauwingen in meerdere kransslagaders.[1] De studie onderzocht of het acuut aanvullend dotteren van alle vernauwde vaten meerwaarde heeft boven het dotteren van alleen het aangedane, 'schuldige' vat (de 'culprit'). De studie is vroegtijdig gestopt omdat het positieve effect op de primaire uitkomstmaat fors was.[1]

Tegenwoordig ondergaan patiënten met een acuut hartinfarct een dotterbehandeling van de acuut afgesloten kransslagader.[2] Bij ongeveer de helft van deze patiënten zijn er daarnaast ook andere vernauwingen, die geen relatie hebben met het acute hartinfarct. Patiënten met meervatslijden hebben een slechtere prognose dan patiënten met eenvatslijden van de kransslagaders.[3] Uit meerdere retrospectieve studies blijkt dat aanvullend dotteren van andere vaten in de acute fase mogelijk samenhangt met een toename van hartinfarcten en een slechtere prognose.[4] Aanvullende revascularisatie wordt daarom pas later verricht, afhankelijk van klachten en diagnostiek naar ischemie.[2,4]

De uitkomst van de PRAMI-studie is dus opmerkelijk. Voor het eerst suggereren onderzoekers dat dotteren van alle vernauwingen in de acute fase wél tot een betere prognose leidt. Als dotterbehandelingen voortaan op basis van deze resultaten uitgevoerd worden, betekent dat een trendbreuk met de huidige gang van zaken. De uitkomst staat in contrast met de ervaring van elke interventiecardioloog. Laten intuïtie en ervaring ons hier in de steek? Of moeten we de resultaten van de PRAMI-studie met een korrel zout nemen?

TWIJFELACHTIG EFFECT VAN MEERVATSLIJDEN OP DE PROGNOSE

Het is bekend dat de prognose voor patiënten slechter is naarmate het coronarialijden uitgebreider is.[3] Een grote studie heeft aangetoond dat electieve dotterbehandeling voor stabiele angina pectoris niet leidt tot een betere prognose maar, bij bewezen ischemie, wel tot een afname van de klachten.[5,6] Recent onderzoek liet zien dat bij patiënten met een acuut hartinfarct en meervatslijden, de slechtere prognose bijna volledig gedreven wordt door de aanwezigheid van een andere oude chronische totale occlusie; vanwege zijn complexiteit wordt deze afwijking nooit in de acute fase behandeld. Patiënten met meervatslijden zonder chronische totale occlusie hebben een vergelijkbare prognose en hartfunctie als patiënten met eenvatslijden.[7]

In de PRAMI-studie wordt gesproken van meervatslijden bij vernauwingen van > 50%, die ter plekke angiografisch werden bepaald. We weten echter dat niet elke af-

wijking > 50% resulteert in ischemie. Het dotteren van angiografische vernauwingen > 50% is onnodig en leidt tot overbehandeling. Daarom wordt tegenwoordig pas een dotterbehandeling uitgevoerd bij afwijkingen > 70%. Nog beter is dat pas te doen na een intracoronaire drukmeting over de vernauwing, wat een objectieve maat is voor de hemodynamische ernst ervan. Deze methode heet 'fractional flow reserve' (FFR).[8]

ONJUISTE PRIMAIRE UITKOMSTMATEN

De primaire uitkomstmaat van de PRAMI-studie was samengesteld uit cardiale dood, niet-fataal myocardinfarct en refractaire angina pectoris. Het ligt voor de hand dat patiënten die na de primaire behandeling nog andere vernauwingen in de kransslagaderen hebben, vaker angina pectoris ontwikkelen. Hierdoor zullen patiënten bij wie alleen het aangedane vat is gedotterd vaker een nieuwe dotterbehandeling nodig hebben. Bij de uitkomstmaat 'niet-fatale hartinfarcten' maakt het studieprotocol geen onderscheid tussen spontane hartinfarcten en hartinfarcten die gerelateerd zijn aan de procedure. Elke troponinestijging > 99ste percentiel met angina pectoris wordt in deze studie als een hartinfarct geteld. Bij electieve percutane procedures treedt er bij 30% van de patiënten een dergelijke troponinestijging op. Aangezien procedurele infarcten in de groep die preventief percutane coronaire interventie (PCI) kreeg niet gedetecteerd kunnen worden door de hoge enzymuitstoot van het initiële infarct, is het bijna bedrieglijk om ze in de conservatief behandelde groep te tellen als eindpunt. Bovendien zijn procedurele hartinfarcten niet geassocieerd met een slechtere prognose, wat wel zo is bij spontane hartinfarcten.

Daarnaast blijft het de vraag of spontaan optredende hartinfarcten wel gelokaliseerd zijn in een onbehandelde vernauwing van > 50%.[9] Een recente studie heeft namelijk aangetoond dat bij patiënten met een acuut coronair syndroom het merendeel van de vernauwingen die uiteindelijk tot een myocardinfarct leidden waarvoor additionele dotterbehandeling noodzakelijk was, juist < 50% waren.

Kortom, een conservatieve PCI-strategie leidt per definitie tot een hogere frequentie van angina pectoris waarvoor weer een PCI wordt gedaan die dikwijls gepaard gaat met een procedureel infarct. Een betere gecombineerde primaire uitkomstmaat zou zijn: cardiale dood en niet-fatale spontane hartinfarcten. Dan zou wel een veel grotere studie nodig zijn.

EFFECTOVERSCHATTING EN PUBLICATIEBIAS

Het grote maar net niet significant effect van preventieve PCI op cardiale dood deed veel stof opwaaien. De kans is echter groot dat dit effect op toeval berust. De PRAMI-studie had onvoldoende power voor de separate onderdelen van de samengestelde primaire uitkomstmaat en de studie is ook nog voortijdig afgebroken na inclusie van ongeveer 75% van de beoogde patiënten. Studies die vroegtijdig worden afgebroken door een onverwacht groot behandelingseffect, overschatten vaak de effectgrootte, voornamelijk wanneer het aantal events in absolute zin laag is.[10] Een paar events hebben dan namelijk al een groot effect op de p-waarde. In totaal waren er 4 cardiale doden in de preventieve PCI-groep (n = 234) en 10 cardiale doden in de groep zonder preventieve PCI (n = 231). Het is gebleken dat positieve studies die voortijdig zijn gestopt gemakkelijker gepubliceerd worden in wetenschappelijke bladen met een hoge impactfactor waardoor ze vaak meer aandacht krijgen dan verdiend.[10]

TOEKOMSTPERSPECTIEF

Er lopen momenteel 3 studies waarin de waarde van aanvullende revascularisatie bij patiënten met een acuut hartinfarct en meervatslijden wordt bestudeerd. In de EXPLORE-studie worden patiënten met een acuut hartinfarct (n = 300) geïncludeerd die naast de acute occlusie ook een oude chronische occlusie hebben. Deze patiënten worden gerandomiseerd naar percutane behandeling van de chronische occlusie binnen 1 week versus een conservatief beleid. De primaire uitkomstmaat is linkerventrikelfunctie en -volume, gemeten met MRI. De COMPARE-ACUTE-studie zal 885 patiënten randomiseren tussen PCI op geleide van FFR binnen 72u en PCI van alleen het aangedane vat. Electieve additionele PCI van vernauwingen die niet gerelateerd zijn aan het infarct vinden plaats op basis van klachten en non-invasieve ischemietesten. De uitkomstmaat is samengesteld uit dood, niet-fataal hartinfarct en elke revascularisatie of cerebrovasculaire event binnen 12 maanden. De COMPLETE-trial is vergelijkbaar met de PRAMI-studie maar zal 3900 patiënten includeren met als primaire uitkomst: cardiovasculaire mortaliteit of een nieuw hartinfarct.

CONCLUSIE

Zet de PRAMI-studie de deur op een kier om alle vernauwingen in de kransslagaders te gaan dotteren in de acute fase? Voorlopig niet!

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Chapter 11

Angioplasty on All Lesions in Case of Myocardial Infarction? Not For the Time Being

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New England Journal of Medicine 2014 Jan,16;(3):281

ABSTRACT

Treatment for acute myocardial infarction currently entails immediate percutaneous revascularization of the culprit artery. Around 50% of the patients with an acute myocardial infarction have additional multivessel coronary artery disease. Patients with multivessel disease are known to have a worse prognosis compared to patients with single vessel disease. Also, immediate additional revascularization in the acute phase has not been associated with improved outcome but with more complications. In the current practice guidelines, additional revascularization is contra-indicated in the acute phase and only warranted in case of persistent symptoms or ischaemia after the acute event. Elective PCI resolves symptoms but its impact on prognosis is less evident. The outcome of the PRAMI trial claims that percutaneous coronary intervention (PCI) of all > 50% lesions improves prognosis. This seems unrealistic. We believe that the study design with a composite endpoint that incorporates the normal treatment strategy ensures a positive outcome but without clinical significance.

LETTER TO THE EDITOR

With great worry we read the report by Wald et al.[1] The primary end point was determined by the clinical treatment strategy itself and therefore does not reflect the clinical benefit of one treatment over the other. Refractory angina was an outcome measure and driven by stenosis, which had been left untreated in patients who did not undergo preventive PCI. It is to be expected that more PCIs were performed in patients in the control group as a consequence of the treatment strategy itself. The definition of myocardial infarction includes both spontaneous and procedural myocardial infarction. Procedural myocardial infarctions that occur during preventive PCI cannot be captured, since they are overshadowed by increases in enzyme levels associated with the index infarction. Moreover, an elevation in the troponin level to more than the 99th percentile occurs in approximately 30% of elective PCIs and will be counted as a myocardial infarction.[2] In contrast to spontaneous myocardial infarction, procedural myocardial infarctions are not associated with increased mortality.[3] In summary, the strategy of no preventive PCI results by definition in a higher rate of angina, associated PCIs, and procedural myocardial infarctions. It is inappropriate to include outcome measures driven by the strategy into the primary end point.

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Chapter 12

Rationale and Design of EXPLORE: a Randomized, Prospective, Multicenter Trial Investigating the Impact of Recanalization of a Chronic Total Occlusion on Left Ventricular Function in Patients after Primary Percutaneous Coronary Intervention for Acute ST-Elevation Myocardial Infarction

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Trials 2010 Sep;11:89

ABSTRACT

Background

In the setting of primary percutaneous coronary intervention, patients with a chronic total occlusion in a non-infarct related artery were recently identified as a high-risk subgroup. It is unclear whether ST-elevation myocardial infarction patients with a chronic total occlusion in a non-infarct related artery should undergo additional percutaneous coronary intervention of the chronic total occlusion on top of optimal medical therapy shortly after primary percutaneous coronary intervention. Possible beneficial effects include reduction in adverse left ventricular remodeling and preservation of global left ventricular function and improved clinical outcome during future coronary events.

Study Design

The Evaluating Xience V and left ventricular function in Percutaneous coronary intervention on occLusiOns afteR ST-Elevation myocardial infarction (EXPLORE) trial is a randomized, prospective, multicenter, two-arm trial with blinded evaluation of endpoints. Three hundred patients after primary percutaneous coronary intervention for ST-elevation myocardial infarction with a chronic total occlusion in a non-infarct related artery are randomized to either elective percutaneous coronary intervention of the chronic total occlusion within seven days or standard medical treatment. When assigned to the invasive arm, an everolimus-eluting coronary stent is used. Primary endpoints are left ventricular ejection fraction and left ventricular end-diastolic volume assessed by cardiac Magnetic Resonance Imaging at four months. Clinical follow-up will continue until five years.

Discussion

The ongoing EXPLORE trial is the first randomized clinical trial powered to investigate whether recanalization of a chronic total occlusion in a non-infarct related artery after primary percutaneous coronary intervention for ST-elevation myocardial infarction results in a better preserved residual left ventricular ejection fraction, reduced end-diastolic volume and enhanced clinical outcome.

Trial registration: trialregister.nl NTR1108.

BACKGROUND

Treatment of patients with acute ST-elevation myocardial infarction (STEMI) aims at early restoration of antegrade flow in the infarct related coronary artery in order to preserve myocardial function and improve survival. Angiography after thrombolysis or before primary percutaneous coronary intervention (PCI) has revealed that multivessel disease (MVD) is present in 40-65% of all STEMI patients. These patients are considered to be a subgroup with a high risk for morbidity and mortality, compared with patients with single vessel disease (SVD).[1,2] An aggressive multivessel PCI strategy during and after primary PCI for STEMI has not improved outcome in MVD patients. In fact, studies reported that treatment of non-culprit lesions in STEMI patients with MVD is associated with a higher post-procedural morbidity rate without improving survival.[3-5] In the setting of primary PCI it was recently demonstrated that, the higher mortality in patients with MVD is mainly determined by the presence of a chronic total occlusion (CTO) in a non-infarct related artery (IRA).[6-10] Furthermore, a CTO in a non-IRA was associated with a reduced left ventricular function during hospitalization for the index event and a further reduction in left ventricular function during follow-up.[6] Therefore, STEMI patients with a CTO constitute the MVD patient group with a truly higher risk for death.[6-9] The ongoing Evaluating Xience V and left ventricular function in PCI on occLusiOns afteR STEMI (EXPLORE) trial is the first randomized clinical trial powered to investigate clinical outcome after percutaneous treatment of a CTO. There are two main mechanisms involved in the hypothesis of the Explore trial. First, recanalization of the CTO will possibly restore the contractile function of the hibernating myocardium. Furthermore, recanalization of the CTO might improve the healing of the infarct border zone. This assumption is based on the coronary anatomy where the perfusion area of the infarct related coronary artery and the CTO are adjacent or overlapping. In recently perfused myocardium, the revascularization of a CTO will improve the myocardial perfusion in this overlapping region and therefore might improve the healing of this border zone and might protect against negative remodelling and preserving residual left ventricular function.

The EXPLORE trial will determine whether recanalization of a CTO within one week after primary PCI for STEMI results in a better preserved residual left ventricular ejection fraction and reduced end-diastolic volume.

METHODS

Overview

The investigator-initiated EXPLORE trial is a prospective, randomized, two-arm trial with blinded evaluation of endpoints. European and North-American high volume primary

PCI centers with a 1.5 Tesla cardiovascular magnetic resonance imaging (cMRI) facility participate in this global trial. The study was first approved by the Medical Ethics Committee on human research at the Academic Medical Center-University of Amsterdam, the Netherlands. For all the foreign centers, the study must be approved by the Medical Ethics Committee on human research in each of the corresponding countries before participation. The study will be conducted in accordance with the declaration of Helsinki. The EXPLORE trial was registered on 30-10-2007 at www.trialregister.nl with trial ID NTR1108.[11]

After successful primary PCI for STEMI, patients with a CTO in a non-infarct related artery are randomized to either elective PCI of the CTO within seven days after primary PCI or to standard medical treatment. Figure 1 shows the flow chart of the trial.

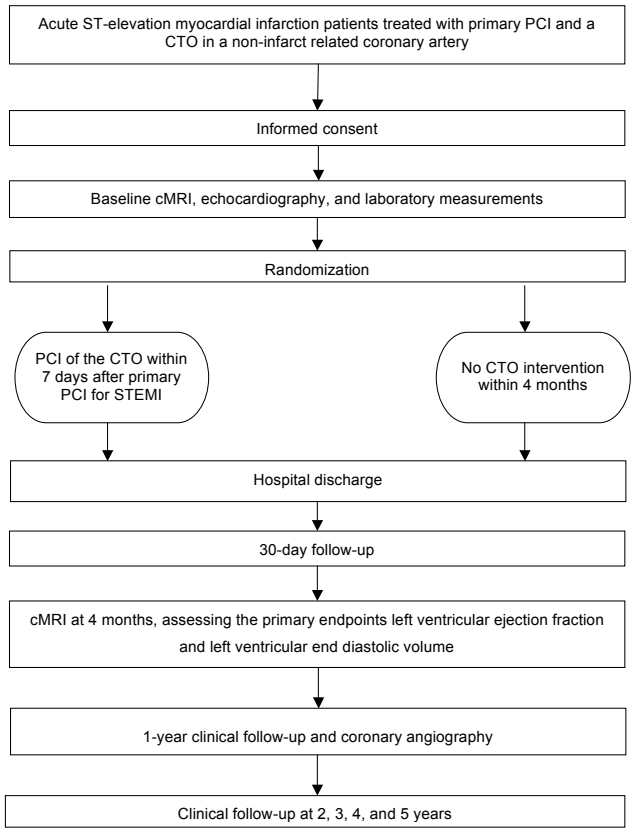

Figure 1. Flow chart of the EXPLORE trial.
STEMI= ST elevation myocardial infarction PCI= Percutaneous Coronary Intervention CTO= Chronic Total Occlusion.

Patients and Enrolment

Consecutive STEMI patients after successful primary PCI, defined as a residual stenosis of the culprit lesion < 30% and a TIMI flow ≥ 2, are screened for entry into the EXPLORE trial. Patients are suitable for inclusion if coronary angiography preceding the primary PCI reveals at least one CTO, situated in a non-infarct related coronary artery or its side branches. For the purpose of this trial, a CTO is defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels. Furthermore, the CTO should be amenable to percutaneous treatment and must be located in a coronary vessel with a reference diameter of at least 2.5 millimeters. All inclusion and exclusion criteria are summarized in Appendix A and B, respectively.

If all inclusion and none of the exclusion criteria are met, the patient is asked for written informed consent, as required by the institutional review board in accordance with the Declaration of Helsinki.

Randomized Treatment Assignment

After informed consent has been obtained, the local investigator contacts the EXPLORE website (www.explorerandomization.org) for online randomization. Patients are randomly assigned following a computer-generated list in a 1:1 ratio to either PCI of the CTO within seven days after the primary PCI or to standard medical treatment.

PCI of the CTO(s)

All PCI procedures are performed under the local routine protocols. All angiograms are recorded in such a way that they are suitable for off-line quantitative coronary angiography (QCA). For patients randomized to PCI of the CTO, the procedure is planned as soon as possible after randomization, but at the latest within seven days after the primary PCI. An approved drug eluting stent is used during PCI of the CTO. For the purpose of uniformity in this trial, the investigators intend to use an everolimus eluting stent (EES) in order to study the performance of the EES in this type of lesion with a high risk of restenosis. Routine electrocardiography and blood analysis including cardiac enzymes are performed before and after PCI of the CTO and are repeated at discharge. Patients randomized to this treatment arm receive clopidogrel 75 mg daily or prasugrel 10 mg daily for at least 12 months after drug eluting stent placement. [12,13]

Standard Medical Treatment

In patients randomized to standard medical treatment, the non-infarct related CTO should not be approached invasively during the first four months after randomization. If, however an unequivocal indication for revascularization arises, follow-up cMRI should be performed before CTO intervention.

Post-STEMI Treatment for Patients with non CTO co-existing coronary lesions

In view of the weak guideline recommendations [14] and the different local practices, our protocol recommends a conservative approach for non-CTO co-existing lesions in the EXPLORE trial. In order to assess the value of CTO revascularization but in view of current daily clinical practice, the decision of the management of non-CTO co-existing lesions must be made before randomization. This decision is made by the local heart team, which generally consist of an interventional cardiologist and or a cardio-thoracic surgeon. In case it is decided that a non-CTO co-existing lesion should be treated, this additional PCI procedure must be performed within one week after the index STEMI. For patients randomized to recanalize the CTO, this additional PCI procedure will be performed during the same procedure as the CTO lesion is being treated. For patients in the conservative group, this additional PCI for non-CTO co-existing lesions will be scheduled within one week after the index STEMI. After the first week, revascularization is only indicated when clinically and or ischemia driven and is preferably performed after four months.

Post-STEMI Treatment for all Patients

All patients included in this trial are treated according to the current ACC / AHA guidelines regarding post STEMI management specifying treatment with at least 100 mg of aspirin daily, clopidogrel in a dosage of at least 75 mg daily or prasugrel 10 mg daily for at least 12 month after primary PCI, adequate lipid-lowering medication, angiotensin converting enzyme (ACE) inhibitors, and beta-blockers.[12,13]

Follow-up

All patients visit the outpatient clinic at 30 days, four months, and twelve months after primary PCI. Thereafter, patients will be followed-up by means of a telephone call at two, three, four, and five years. During all three follow-up outpatient clinic visits, clinical evaluation with a 12-lead electrocardiogram and an inventory of adverse events is obtained. Adverse events included in this inventory are cardiac and non-cardiac death, stent thrombosis according to the definition of the Academic Research Consortium (ARC)[14] myocardial re-infarction, all cardiac surgery, implantation of an implantable cardioverter-defibrillator device, clinically overt heart failure, repeat coronary angiography and repeat PCI, hospital admission for angina, stroke, and severe bleeding events.

At four months, cMRI is performed in all patients along with routine laboratory measurements and exercise testing. If a contraindication for cMRI has risen because of altered patient characteristics after inclusion, the protocol permits single positron emission computed tomography (SPECT) as a secondary and echocardiography as a tertiary modality for endpoint assessment.

Scheduling of repeat angiography is at the discretion of the treating physician. Repeat angiography is preferably performed at one year after randomization in all patients.

Cardiac Magnetic Resonance Imaging

After written informed consent, baseline cMRI is recommended to be performed at least 48 hours after the primary PCI but before the patient is randomly assigned to one of the treatment arms. All patients undergo cMRI at four-month follow-up to assess the primary endpoints of this trial. Patients are studied on a clinical 1.5-Tesla scanner using a 4-element phased array cardiac receiver coil. For functional imaging, electrocardiogram-gated cine steady-state, free-precession magnetic resonance images are obtained during repeated breath holds in the 3 standard long-axis views (4 -, 3- and 2-chamber view). Additional short-axis slices are acquired, covering the entire left ventricle from base to apex, to examine regional and global left ventricular function. Late contrast–enhanced (LCE) images are acquired 10 minutes after administration of a gadolinium-based contrast agent with an inversion recovery, gradient-echo pulse sequence to identify the location and extent of myocardial infarction. The data are obtained with slice locations identical to the functional images. All MRI images are sent to an independent core laboratory for quality control and blinded central analysis. On the short axis cine slices, the endocardial and epicardial borders are outlined manually in end-diastolic and end-systolic images, excluding trabeculae and papillary muscles. Assessment of global left ventricular function is obtained by calculating left ventricular volumes, mass, and ejection fraction using the summation of slice method multiplied by slice distance.

Primary Endpoints

The two primary endpoints of this trial are differences between the two treatment arms in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV), assessed by cMRI at four months after primary PCI for STEMI, Appendix C.

Safety and Other Secondary Endpoints

Safety will be determined by the assessment of Major Adverse Coronary Events (MACE) defined as cardiac death, peri-procedural myocardial infarction, myocardial infarction or any repeat coronary intervention at 30 days, 4 months and 1, 2, 3, 4, 5 years. Furthermore, safety is also determined by the occurrence of stent thrombosis. All safety endpoints are defined in accordance with the ARC. [14] The trial will be monitored by a Data and Safety Monitoring Board (DSMB) and the trial will be discontinued in case of safety concerns. All other secondary endpoints are displayed in Appendix C.

A pre-specified subgroup analysis will be performed in which the primary outcome, Major Adverse Coronary Events (MACE) and suitable other secondary endpoints will be stratified according to the presence of non-CTO co-existing lesions.

Statistical Considerations

Both primary and all secondary endpoints are displayed in Appendix C. As this study has two primary endpoints, the Hochberg extension of the Bonferroni method for multiple comparisons will be used to test for statistical significance with an overall type I error rate less than or equal to 0.05. [15] The statistical comparisons of the treatment arms with respect to the primary and secondary endpoints are performed using the independent-samples T-test, or Fisher's exact probability test in case of binary endpoints. All p-values are 2-sided. For clinical outcomes such as the incidence of major adverse cardiac events, Kaplan-Meier curves displaying the pattern of events over the four-month and one-year follow-up period are constructed. Statistical significance and 95-% confidence intervals are calculated using Cox' proportional hazards model.

The trial is powered to detect differences between the two groups in cMRI assessed LVEF and LVEDV at four months after STEMI. With 2 x 150 randomized patients, this trial has an 80% power to detect absolute differences of 4% in LVEF and 15mL in LVEDV in favor of PCI of the CTO with a one-sided alpha of 5%. For this calculation we have assumed that PCI of a CTO is successful in 80% of cases. The mean global ejection fraction in patients with an untreated CTO is assumed to be 36% against 40% in patients with successful CTO treatment with a common standard deviation of 12%. Consequently, the expected global ejection fraction is 40% (0.8 x 41% + 0.2 x 36%) in patients randomized to CTO treatment against 36% in patients randomized to standard medical treatment. The calculation for the second primary endpoint is based on the assumption of a net mean LVEDV of 185 ml for patients randomized to CTO treatment and of 200 ml for patients randomized to standard medical treatment. The standard deviation for LVEDV was assumed to be 45 ml. Patients who have deceased before primary endpoint measurement will be attributed the lowest LVEF and the largest LVEDV measured in the whole study cohort. The primary endpoint will be analyzed on an intention-to-treat basis.

Study Organization and Monitoring

An executive committee will supervise the EXPLORE trial, while a study coordination committee will coordinate the trial and perform QCA analysis. The steering committee is responsible for design and conduct of the study. An independent data and safety monitoring board watches over the ethics of conducting the study in accordance with the Declaration of Helsinki, monitors the patient safety, and reviews safety issues as the study progresses. All major adverse cardiac events will be adjudicated by a Critical Events Committee. The specific role and information regarding each of the committees appear in appendix D.

DISCUSSION

Prognosis after primary PCI

After primary PCI for acute STEMI, patients with MVD have a worse clinical outcome when compared to patients with SVD.[1,2,6,16] Previous randomized studies investigating multivessel PCI during the primary procedure or shortly thereafter have been hampered by small patient numbers and have failed to show clinical benefit of additional revascularization after primary PCI.[17,18] Furthermore, a number of observational studies investigating the value of additional revascularization after primary PCI have reported inconclusive results.[3-5,19-21]

Recently, we reported that patients with a CTO in a non-IRA are the subgroup of MVD patients who are truly at risk after primary PCI for STEMI.[6,8] A CTO in a non-IRA was a strong and independent predictor of 30-day, 1-year, and 5-year mortality whereas MVD without a CTO was only a weak predictor of 30-day mortality, and not an independent predictor of 1-year, and 5-year mortality. We reported similar results in a cohort consisting exclusively of STEMI patients with cardiogenic shock.[9] Furthermore, a CTO in a non-IRA was associated with reduced LVEF during the index hospitalization and a further reduction in LVEF within the first year thereafter.[6] Therefore, rather than a significant diseased concomitant coronary artery, a CTO in a non-IRA is a target for additional revascularization after primary PCI.

These findings drive the rationale behind the EXPLORE trial. Recanalization of a CTO in a non-IRA shortly after primary PCI may improve regional myocardial function and promote infarct healing at the border zones. These effects may attenuate the remodeling process, which may lead to a better preserved residual global LV function, decreased LVEDV, and improved survival. This trial will be the first to prospectively determine the effect of PCI of a CTO in a non-IRA in the early recovery phase after successful primary PCI for STEMI on LV performance.

LV function after elective PCI of a CTO

LVEF and LVEDV are major prognostic determinants in patients with coronary artery disease. It is suggested that opening of CTO's in an elective setting can be of benefit by restoring blood flow to hibernating myocardium and thus improving LV function. Improvement of LV function and a reduction of both end-diastolic and end-systolic volume after recanalization of a CTO has been demonstrated in several studies, provided long-term patency could be achieved.[22-25]

PCI of a CTO: higher risk of restenosis

Percutaneous recanalization of a CTO amenable to PCI treatment can be performed with a success rate of 70-80%, but is associated with a higher rate of restenosis compared

to PCI of non-occluded vessels. Although coronary stenting has been shown to be superior to conventional balloon angioplasty, restenosis rates remain relatively high. When compared to bare metal stents, drug eluting stents (DES) are effective in decreasing the need for repeat intervention in successfully treated CTO patients.[26] However, there have been concerns about long-term delay of arterial healing as a consequence of both Sirolimus eluting stent (SES) and Paclitaxel eluting stent (PES) placement and the associated risk of late stent thrombosis. Both preclinical and clinical data for a second-generation DES, the EES, are encouraging in terms of arterial healing and low restenosis rates. The EES showed superior endothelialization compared with the PES, SES and Zotarolimus-eluting stent at 14 days after stent implantation.[27] This suggests a superior safety profile for the EES, as shown in the one-year results of the SPIRIT IV trial, randomizing 3687 patients in a 2:1 fashion to either the EES or the PES for treatment of patients with de novo coronary artery disease with a maximum of 3 lesions. The SPIRIT IV investigators reported a 0.29% ARC definite or probable stent thrombosis rate in the EES arm, as compared to 1.1% in the PES arm (p=0.003). Furthermore, the EES performed superior over the PES regarding ischemia-driven target lesion revascularization, (3.9% vs 6.6%, p=0.0008).[28] Although extensively studied in relatively low-risk lesions, currently data regarding the performance of the EES in CTO's are lacking.

To conclude, no clinical trial to date has investigated the effect of percutaneous recanalization of CTO's on clinical endpoints in any setting. The high case-fatality rates and inferior recovery of LV function after STEMI of patients with a CTO in a non-IRA provide the rationale for the current trial. The ongoing EXPLORE trial is the first randomized clinical trial powered to investigate clinical outcome after percutaneous treatment of a CTO. The Explore trial will determine whether recanalization of a CTO within one week after primary PCI for STEMI results in a better preserved residual left ventricular ejection fraction and reduced end-diastolic volume.

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APPENDIX A

Inclusion criteria EXPLORE trial	
Patients are eligible for inclusion if all of the inclusion criteria are met:	
	• Successful primary percutaneous coronary intervention[1] for acute ST elevation myocardial infarction[2]
And	• Presence of at least one chronic total occlusion located in a non-infarct related coronary artery, defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels
And	• Reference diameter of ≥2.5 millimeters
And	• Amenable to treatment by percutaneous coronary intervention

1 Residual stenosis of the culprit lesion < 30% and Thrombolysis In Myocardial Infarction flow ≥ 2.
2 definition according to Alpert et al. Myocardial infarction redefined – a consensus document of The joint ESC / ACC committee for the redefinition of myocardial infarction.[29]

APPENDIX B

Exclusion criteria EXPLORE trial.
Age > 80 years
Persistent or permanent atrial fibrillation
Known renal insufficiency (serum creatinin > 265 µmol/L or >3.5 mg/L)
Persistent hemodynamic instability[1] lasting up to 48 hours after primary PCI
Cardiac events[2] between primary PCI and randomization
Significant left main stenosis (diameter stenosis ≥ 50%)
Severe coronary artery disease, not amenable for PCI but suitable for coronary artery bypass grafting
Severe valvular heart disease requiring cardiac surgery within four months
Clinically driven indication for implantable cardioverter defibrillator within four months
Inability to schedule the index procedure within seven days after primary PCI
Contraindication for cMRI (i.e. pacemaker, cerebrovascular clips, or claustrophobia)
Serious known concomitant disease with a life expectancy of less than one year
Circumstances that prevent follow-up
Previous participation in this trial or any other trial within the previous 30 days
1 Defined as pre-shock (heart rate > 100/min, and/or systolic blood pressure < 100mm Hg) or shock
2 Defined as extended myocardial infarction, acute stent thrombosis, or late (>48 hours after primary PCI) and life threatening ventricular arrythmias

PCI= Percutanous Coronary Intervention, cMRI= cardiovascular Magnetic Resonance Imaging.

APPENDIX C

EXPLORE trial endpoints.
Primary Endpoints Measured by cardiovascular magnetic resonance imaging at 4 months:
- Left ventricular ejection fraction
- Left ventricular end-diastolic volume
Secondary Endpoints
Safety Endpoints
Major Adverse Cardiac Events, defined as cardiac death, myocardial infarction or any repeat coronary intervention* at 30 days, 4 months, and 1, 2, 3, 4, and 5 years
Stent thrombosis, classified as definite, probable or possible Other Secondary Endpoints
Measured by cardiac magnetic resonance imaging at 4 months:
- Left ventricular end-systolic volume - Left ventricular segmental wall thickening
- Left ventricular mass - Infarct size (by late contrast enhancement)
N Terminal – pro Brain Natriuretic Peptide (at 4 months and 1 year, relative to baseline)
Heart rate-adjusted QT (QTc) duration measured by resting electrocardiography (at 4 months and 1 year, relative to baseline)
Quantitative Coronary Angiography of the treated chronic total occlusions:
- in-stent and in-segment late luminal loss at 12 months
- in-stent and in-segment minimal luminal diameter
- in-stent and in-segment binary restenosis rate
Repeat Hospitalization for cardiac causes at 30 days, 4 months, and 1, 2, 3, 4, and 5 years
Presence of clinically overt heart failure at 30 days, 4 months, and 1, 2, 3, 4, and 5 years
Implantation of implantable cardioverter-defibrillator devices
Functional Class: NYHA classification at 30 days, 4 months, and 1, 2, 3, 4, and 5 years
*Excluding the initial percutaneous coronary intervention of the chronic total occlusion when randomly assigned to this treatment arm. MRI: Magnetic resonance imaging NYHA: New York Heart Association

APPENDIX D

Executive Committee

The Executive Committee will be composed of the study principal investigators and selected members among the investigators. This committee is responsible for overseeing the administrative progress of the study and approval of the final trial design and protocol issued to the DSMB and the clinical sites. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selecting the secondary projects and publications by members of the Steering Committee. The executive committee also holds the right to modify or stop the study prematurely based on recommendations from the DSMB.

Steering Committee

The Steering Committee will be composed of the principal investigators from the participating centers in this trial. The Steering Committee is responsible for the day-to-day administrative management of the trial and will meet on a monthly basis to monitor subject enrollment, clinical site progress and protocol compliance. It will be the responsibility of the Steering Committee to provide assistance and education to individual sites and researchers to help with trial management, record keeping, and reporting requirements.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be composed of general and interventional cardiologists and a biostatistician. The DSMB will function in accordance with applicable regulatory guidelines. The board members are independent and will not be participating in the trial. The DSMB will review the safety data from this trial and will make recommendations based on safety analyses of unanticipated device effects, serious adverse events, protocol deviation, and device failures. The DSMB will meet annually; in addition, the DSMB may meet at any time if there is reason to suspect that safety is an issue. The DSMB is responsible for making recommendations regarding any safety or compliance issues throughout the course of the study and may recommend to the Executive Committee to modify or stop the study. However, all final decisions regarding study modifications rest with the Executive Committee. All cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout enrollment and follow-up periods to ensure patient safety. Every effort will be made to allow the DSMB to conduct an unbiased review of patient safety information. The DSMB will develop a consensus understanding of all trial endpoints and definitions used in the event adjudication process. All DSMB reports will remain strictly confidential but will be made available to the regulatory body upon request.

Critical Events Committee

The Critical Events Committee (CEC) consists of two experienced clinical cardiologist who will not participate in the trial. The CEC will adjudicate all major adverse cardiac events in this trial as specified by the study protocol. Both members of the CEC will be blinded to the primary results of the trial.

Chapter 13

The Impact of Percutaneous Intervention for Concurrent Chronic Total Occlusion on Left Ventricular Function in ST-Elevation Myocardial Infarction (EXPLORE): a Randomized Multicenter Trial

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Submitted to Journal of the American College of Cardiology

ABSTRACT

Background

In 10% of patients with ST-elevation myocardial infarction (STEMI) a concurrent chronic coronary total occlusion (CTO) in a non-infarct related artery (IRA) is present, which is associated with increased morbidity and mortality.

Objectives

To evaluate if STEMI patients with a concurrent CTO in a non-IRA benefit from additional percutaneous coronary intervention (PCI) of the CTO shortly after primary PCI.

Methods

From November 2007 through April 2015, we enrolled 304 patients with acute STEMI who underwent primary PCI and had a concurrent CTO in 14 centers in Europe and Canada. A total of 150 patients were randomly assigned to early PCI of the CTO (CTO-PCI) and 154 patients to conservative treatment without PCI of the CTO (No CTO-PCI). Primary outcomes were left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) on cardiovascular magnetic resonance imaging (CMR) after 4 months.

Results

Investigator reported procedural success rate in the CTO-PCI arm was 77% and adjudicated success rate was 73%. At four months, mean LVEF did not differ between the CTO-PCI and the No CTO-PCI arm; 44.1±12.2% vs 44.8±11.9%, respectively, p=0.60. Mean LVEDV at four months was 215.6±62.5ml in the CTO-PCI arm vs. 212.8±60.3ml in the No CTO-PCI arm, p=0.70. A subgroup analysis revealed that patients with a CTO located in the left anterior descending coronary artery (LAD) randomized to the CTO-PCI strategy had significantly higher LVEF compared with patients randomized to the No CTO-PCI strategy (47.2±12.3% vs. 40.4±11.9%, p=0.02). There were no differences in terms of four-month MACE (5.4% vs. 2.6%, p=0.25).

Conclusions

Additional CTO-PCI within one week after primary PCI for STEMI was feasible and safe. In STEMI patients with a concurrent CTO we did not find an overall benefit for CTO-PCI in terms of LVEF or LVEDV. The finding that early CTO-PCI in the LAD subgroup was beneficial warrants further investigation.

INTRODUCTION

Patients with acute ST-segment elevation myocardial infarction (STEMI) are effectively treated with immediate percutaneous coronary intervention (PCI) to restore blood flow to the acutely occluded infarct related coronary artery.(1-4)Approximately half of these patients are identified with additional flow limiting stenoses in non-infarct related coronary arteries, often referred to as multivessel coronary artery disease (MVD). These patients exhibit a twofold higher morbidity and mortality compared with patients with single vessel disease.(5,6) The most severe expression of coronary artery disease is a chronic total occlusion (CTO). A growing body of evidence suggests that the excess morbidity and mortality in MVD patients, compared with single vessel disease, is mainly explained by the presence of a concurrent CTO.(7,8) Concurrent CTOs are found in around 10-15% of STEMI patients.(7,8) Several observational studies suggest that percutaneous revascularization of CTO lesions leads to higher left ventricular ejection fraction (LVEF), a reduced need for coronary artery bypass graft surgery (CABG) and improved survival. (9,10) Because of the procedural complexity and below average success rate, PCI is only attempted in 10% of all CTOs, commonly in an elective setting.(11)

The Evaluating Xience and left ventricular function in PCI on occlusiOns afteR STEMI (EXPLORE) trial is the first randomized clinical trial powered to investigate functional outcome after percutaneous treatment of a CTO found during primary PCI for STEMI. There are two main mechanisms involved in the hypothesis of the Explore trial. First, recanalization of the CTO may restore the contractile function of the hibernating myocardium. Furthermore, recanalization of the CTO may improve the healing of the infarct border zone, especially where the perfusion area of the infarct related coronary artery and the CTO are adjacent or overlapping. We hypothesize that early revascularization of a CTO improves myocardial perfusion in these overlapping territories, protecting against negative remodeling.

In the EXPLORE trial, we test the hypothesis that early, routine PCI of a concurrent CTO found during primary PCI for STEMI improves LVEF and reduces left ventricular end-diastolic volume (LVEDV), measured by cardiovascular magnetic resonance imaging (CMR) after 4 months.

METHODS

Study design

The EXPLORE study was an investigator-initiated, prospective, multicenter, international, randomized, two-arm trial with blinded evaluation of endpoints. European and North-American high volume primary PCI centers with a 1.5 Tesla CMR facility participated in

this global trial. The trial protocol, as approved in Amsterdam by a central ethics committee, has previously been published.(12) Ethics committee approval was received in all participating centers, according to local regulations.

The study was conducted in accordance with the declaration of Helsinki. The EXPLORE trial was registered on 30-10-2007 at http://www.trialregister.nl with trial ID NTR1108. A steering committee provided oversight of the trial, and a data and safety monitoring board (DSMB) advised on whether the trial should be stopped because of clear evidence of benefit or harm.

Participants

After electrocardiographic confirmation of STEMI, patients presenting within 12 hours of symptom onset were considered for the trial if they fulfilled all inclusion criteria and did not fulfil any exclusion criteria. Patients were eligible if a concurrent CTO in a non-infarct related artery was found during successful primary PCI for STEMI. Successful primary PCI was defined as a residual stenosis of the culprit lesion < 30% and a TIMI flow ≥ 2. For the purpose of this trial, a CTO was defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels. The CTO should be located in a coronary vessel with a reference diameter of at least 2.5 millimetres. Among the exclusion criteria were hemodynamic instability persisting for >48 hours after primary PCI and factors precluding reliable CMR imaging such as persistent or permanent atrial fibrillation, severe renal insufficiency, and indications for pacemaker or implantable cardioverter-defibrillator implantation. Full inclusion and exclusion criteria

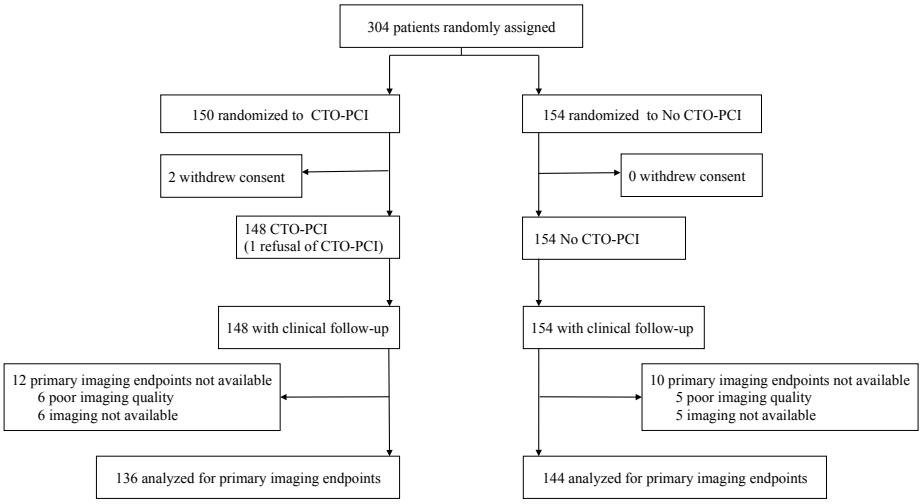

Figure 1: Trial profile.
CTO=chronic total occlusion. PCI=percutaneous coronary intervention.

are summarized in supplementary appendix A and B, respectively. The study protocol mandated a screening echocardiogram to exclude valvular disease requiring surgical treatment. All patients were only eligible upon local heart team approval, including decision making on PCI of any non-CTO lesions**.** Figure 1 shows the flow chart of the trial.

Randomization

After written informed consent had been obtained, patients were randomized to a strategy of additional PCI of the CTO (CTO-PCI) within seven days after primary PCI or to a conservative strategy for at least 4 months (No CTO-PCI). In patients randomized to No CTO-PCI, intervention of the CTO within the first four months was only permitted when clinically driven in the presence of severe symptoms requiring invasive treatment. Randomization was done in an open-label manner with an electronic web-based system in permuted blocks of varying size in each participating center.

Procedures

PCI of the CTO

The technique of the CTO PCI procedure was left to the operator without any restrictions, except for protocol-mandated everolimus-eluting stent (EES) stent use. Successful CTO-PCI was defined as a residual stenosis of the CTO lesion < 30% and TIMI flow ≥ 2 to at least 50% of the territory supplied by the CTO. In patients with multiple CTO lesions, success was defined if at least one CTO was successfully treated. For patients with multiple CTOs, the CTO supplying the largest amount of myocardium was defined as the main CTO.

PCI of non-CTO co-existing coronary lesions

The protocol recommended a conservative approach for non-CTO co-existing lesions, except for those requiring intervention as decided by the local heart team. In patients randomized to CTO-PCI, these lesions were treated during the CTO-PCI procedure. In patients randomized to No CTO-PCI, an extra procedure was scheduled within one week after randomization.

Follow-up, Data Collection, and Cardiovascular Magnetic Resonance Imaging

Clinical follow-up information was obtained at the outpatient clinic were all patients were seen at 1 and 4 months.

At 4 months, a CMR was performed on a 1.5-Tesla scanner using a dedicated phased array cardiac receiver coil. For functional imaging, ECG-gated steady-state free-precession cine images were obtained during repeated breath holds in short-axis orientation covering the left ventricle from base to apex. At least 10 minutes after administration of

a gadolinium-based contrast agent, the late gadolinium-enhanced (LGE) images were acquired using an inversion recovery gradient-echo pulse sequence with slice locations identical to the cine images to identify the size and extent of myocardial infarction. All CMR images were sent to an independent core laboratory (ClinFact Corelab, Leiden) for quality control and blinded central analysis using dedicated software (QMass MR analytical software version 7.6, Medis BV, Leiden).

Data were gathered electronically and were stored on a dedicated, secure server by Med-Base, Zwolle. Trial data were independently monitored by Cordinamo, Wezep. All baseline coronary angiograms, (non) CTO-PCI procedural characteristics, complications and success rates were adjudicated by a dedicated blinded corelab and calculation of SYNTAX scores was performed by Cardialysis, Rotterdam.

Outcomes

The two co-primary endpoints were LVEF and LVEDV, assessed by CMR at 4 months. The short axis cine images were used to measure LVEDV and indexed for body surface area. LVEF was calculated from the LVEDV and LVESV. Patients who died before the 4 months endpoint were attributed the lowest LVEF and largest LVEDV. If CMR was not available primary endpoint parameters were obtained from alternative imaging modalities, preferably from nuclear based imaging or echocardiography. Assessment of primary endpoints using alternative imaging modalities was performed by an independent corelab blinded to other trial data and randomization outcome.

Secondary CMR endpoints were infarct size and regional myocardial function. Infarct size was determined on the LGE images as previously described using a standardized definition of hyperenhancement.(13) Regional myocardial function was assessed by dividing each short-axis slice into 12 equi-angular segments to calculate wall thickening (in millimetre) of each segment by subtracting end-diastolic from end-systolic wall thickness. Myocardial segments were considered dysfunctional if segmental wall thickening was <3mm.(14) Transmurality of scar tissue of the myocardium in the territory supplied by the coronary artery in which the non-IRA CTO was located was assessed in patients who underwent baseline CMR of sufficient quality. The left ventricle was divided into 16 segments according to the AHA model.(15) Whether a segment was supplied by the CTO coronary artery was assessed by the CMR corelab based upon the baseline coronary angiogram.

Periprocedural myocardial infarction was assessed according to the original protocol definition which was identical to the 2007 Academic Research Consortium (ARC) criteria.(16) Additionally, periprocedural myocardial infarction was also adjudicated according to the third universal definition of myocardial infarction.(17)

Major Adverse Coronary Events (MACE) was defined as the composite of cardiac death, myocardial infarction, and coronary bypass graft surgery (CABG). Cardiac death was

defined according to the ARC criteria and myocardial infarction was defined according to the third universal definition of myocardial infarction criteria. PCI was characterized as repeat PCI of the treated CTO lesion, PCI of non-CTO lesions in the CTO vessel, and PCI in non-CTO vessels according to ARC criteria. Stent thrombosis was defined according to ARC. Stent thromboses were assigned to the CTO unless they could unequivocally be associated with a non-CTO lesion.

An independent clinical events committee (CEC) adjudicated all potential cases of periprocedural myocardial infarction, MACE, repeat PCI, stent thrombosis, and all other periprocedural complications.

Statistical analysis

The trial was powered to detect differences between the two groups in CMR-assessed LVEF and LVEDV at four months after STEMI. With 2 × 150 randomized patients, there was 80% power to detect absolute differences of 4% in LVEF and 15mL in LVEDV in favour of PCI of the CTO with a two-sided alpha of 5%. We assumed that CTO PCI would be successful in 80% of cases. The mean global LVEF in patients randomized to the No-CTO strategy was assumed to be 36% against 41% in patients randomized to the CTO-PCI strategy with a common standard deviation of 12%. Consequently, the expected global ejection fraction was 40% (0.8 × 41% + 0.2 × 36%) in patients randomized to CTO-PCI against 36% in patients randomized to No CTO-PCI. The calculation for the second primary endpoint was based on the assumption of a net mean LVEDV of 185 ml for patients randomized to CTO-PCI and of 200 ml for patients randomized to No CTO-PCI. The standard deviation for LVEDV was assumed to be 45 ml. The primary endpoint was analysed on an intention-to-treat basis.

As this study had two primary endpoints, the Hochberg extension of the Bonferroni method for multiple comparisons was used to test for statistical significance with an overall type I error rate ≤0.05.(18) The statistical comparisons of the treatment arms with respect to the primary and secondary endpoints were performed using the independent-samples T-test, or Fisher's exact probability test in case of binary endpoints. All p-values were 2-sided. For the incidence of MACE, Kaplan-Meier curves displaying the pattern of events over the four-month follow-up period were constructed; the log-rank statistic was used to calculate statistical significance.

Role of the funding source

The study was investigator initiated with a research grant provided by Abbott Vascular International. The grant givers had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

From November 2007 through April 2015, 304 patients were enrolled at 14 sites. A total of 150 patients were randomly assigned to the CTO-PCI arm and 154 patients were randomized to the No CTO-PCI arm. Two patients randomized to the CTO-PCI arm withdrew informed consent before CTO-PCI, reducing the CTO-PCI group to 148 patients.

Baseline and procedural characteristics

The study populations in both arms were well balanced without any significant differences in baselines characteristics (Table 1). The most common infarct-related coronary artery was the left anterior descending coronary artery (LAD, n=136, 45%), followed by the right coronary artery (RCA, n=93, 31%) and the circumflex artery (RCX, n=73, 24%). Triple vessel disease was present in 43% of the study population (n=129). Most concurrent CTOs were located in the RCA (n=142, 47%), followed by the RCX (n=85, 28%) and the LAD (n=75, 25%). Transmurality of scar tissue in the myocardial territory supplied by the CTOs was assessed in 149 patients (49.0%), and none of them had >75% transmurality in the CTO territory .

Table 1: Baseline characteristics and discharge medication.

	CTO-PCI (n=148)		**No CTO-PCI (n=154)**	
Age (years, mean, SD)	60	(±10)	60	(±10)
Men	131	(89%)	126	(82%)
Diabetes	22	(15%)	25	(16%)
Hypertension	59	(40%)	69	(45%)
Family history of coronary artery disease	66	(45%)	64	(42%)
Hypercholesterolaemia or on statin	51	(35%)	52	(34%)
Current smoker	77	(52%)	76	(49%)
Previous myocardial infarction	19	(13%)	24	(16%)
Previous PCI	9	(6%)	16	(10%)
Previous stroke	5	(3%)	6	(4%)
Primary PCI				
Infarct related artery				
Right coronary artery	46	(31%)	47	(31%)
Left circumflex artery	30	(20%)	43	(28%)
Left anterior descending artery	72	(49%)	64	(42%)
TIMI flow pre-PCI 0/1	101	(68%)	97	(63%)
TIMI flow post-PCI 2/3	148	(100%)	154	(100%)

Table 1: Baseline characteristics and discharge medication. (continued)

	CTO-PCI (n=148)		No CTO-PCI (n=154)	
Stent placement	146	(99%)	154	(100%)
Drug eluting stent	88	(59%)	103	(67%)
Triple vessel disease (>70% stenosis)	62	(42%)	67	(44%)
MI Syntax Score I (pre-PCI) (mean, SD)	29	(±8)	29	(±10)
MI Syntax Score II (wiring/balloon/aspiration) (mean, SD)	27	(±8)	27	(±10)
Infarct size				
Peak CK-MB (median, IQR)	130	(39-272)	111	(43-256)
Peak Troponine T (median, IQR)	3.1	(1.1-7.8)	3.3	(0.9-6.0)
LVEF prior to randomization (mean, SD)*	41	(±11)	42	(±12)
CTO characteristics during primary PCI (adjudicated)				
Patients with multiple CTOs†	13	(9%)	22	(14%)
CTO related artery				
Right coronary artery	64	(43%)	78	(51%)
Left circumflex artery	48	(32%)	37	(24%)
Left anterior descending artery	36	(24%)	39	(25%)
TIMI flow				
0	132	(89%)	139	(90%)
1	15	(10%)	14	(9%)
2	1	(1%)	1	(1%)
Total J-CTO score (mean, SD)	2	(±1)	2	(±1)
Previously failed lesion	2	(1%)	4	(3%)
Blunt stump	33	(22%)	45	(29%)
Bending	98	(66%)	108	(70%)
Calcification	115	(78%)	132	(86%)
Occlusion length ≥20mm	60	(41%)	68	(44%)
Discharge medication				
Aspirin	148	(100%)	152	(99%)
Clopidogrel/Prasugrel/Ticagrelor	148	(100%)	154	(100%)
Beta-blocker	138	(93%)	139	(90%)
ACE inhibitor or ARB	133	(90%)	121	(79%)
Lipid lowering drugs	144	(97%)	147	(96%)

Data are number of patients (%), unless otherwise stated. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. CK-MB=creatine kinase-MB isoenzyme. CTO=chronic total occlusion. J-CTO=Multicenter CTO registry of Japan. ACE=angiotensin converting enzyme. ARB=angiotensin-II-receptor blocker. MRI =magnetic resonance imaging. *Imaging modality is MRI only, data available in n=201 patients. † For patients with multiple CTOs, the CTO supplying the largest amount of myocardium was defined as the main CTO.

Patients randomized to a CTO-PCI strategy underwent the procedure on average on day 5.0±1.9. One patient randomized to the CTO-PCI arm refused the procedure. Investigator reported procedural success rate in the CTO-PCI arm was 77% and adjudicated success rate was 73%. Procedural characteristics including procedural complications are presented in Table 2. No peri-procedural death or emergency CABG surgery occurred during CTO-PCI.

Table 2: Procedural characteristics in patients undergoing CTO-PCI.

	CTO-PCI (n=147*)		
CTO Treatment			
Number of days from primary PCI to CTO PCI (mean, SD)	5	(±2)	
Number of days from randomization to CTO PCI (mean, SD)	2	(±2)	
Multiple CTO arteries treated	6	(4%)	
Technique CTO procedure			
Antegrade only Retrograde	124	(84%)	
Retrograde	23	(16%)	
Crossboss/ Stingray	5	(3%)	
PCI successful (investigator reported)	113	(77%)	
PCI successful (corelab adjudicated)	108	(73%)	
Stent usage (in patients with successful CTO-PCI, n=106)			
Everolimus eluting stent	95	(90%)	
Other drug eluting stent	11	(10%)	
Number of stents used (median, IQR)	2	(1-3)	
Periprocedural adverse events	**CTO Vessel**		**Donor Artery**
Dissection	12		1
Occlusion side branch	2		0
Thrombus	1		0
Tamponade	1		0
Major arrhythmia†	2		
Resuscitation	4		
Peri-procedural myocardial infarction			
Third universal definition of myocardial infarction	4		
Study protocol‡	13		
Emergency CABG surgery	0		
Stroke	0		
Peri-procedural death	0		

Data are number of patients (%), unless otherwise stated. PCI=percutaneous coronary intervention. CTO=chronic total occlusion. CABG=coronary artery bypass grafting. *1 patient refusal of PCI CTO. † Ventricular fibrillation/ Sustained ventricular tachycardia. ‡Data available in n=71patients.

Primary and secondary CMR endpoints

A total of 136 patients were analysed for the primary endpoints in the CTO-PCI arm and 144 in the No CTO-PCI arm, as elucidated in the flow chart (figure 1). At four months, mean LVEF was 44.1±12.2% in the CTO PCI arm and 44.8±11.9% in the No CTO-PCI arm, p=0.597. Mean LVEDV was 215.6±62.5ml in the CTO-PCI arm vs. 212.8±60.3ml in the No CTO-PCI arm, p=0.703 (figure 2 and table 3). A subgroup analysis showed a strongly significant interaction between randomized treatment assignment and 4-month LVEF in patients with a CTO located in the LAD (p<0.002, figure 3). In patients with a concurrent CTO in the LAD, LVEF was significantly higher in the CTO-PCI arm compared with the No CTO-PCI arm (47.2±12.3% vs. 40.4±11.9%, p=0.02). For the co-primary endpoint of LVEDV there was also a significant interaction between CTO location and randomized treatment assignment (p=0.04, figure 3). Additional subgroup analyses revealed no other significant interactions.

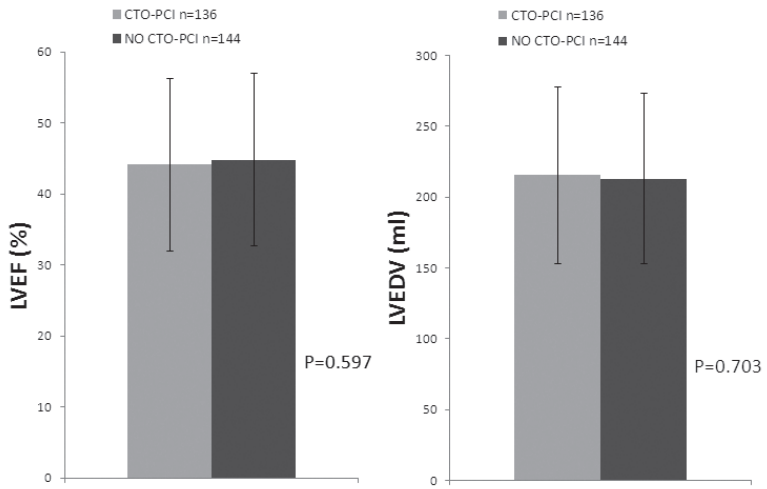

Figure 2: Primary Outcome: Left ventricular ejection fraction (left chart) and left ventricular end diastolic volume (right chart) at four-month follow-up
LVEF= left ventricular ejection fraction, LVEDV= left ventricular end diastolic volume.
CTO= chronic total occlusion, PCI= percutaneous coronary intervention.
Whiskers indicate standard deviation.

Table 3: Imaging outcomes.

	CTO-PCI		No CTO-PCI		Difference (95%CI)		p
Primary endpoint	**(n=136)**		**(n=144)**				
Left ventricular ejection fraction (%)	44.1	(12.2)	44.8	(11.9)	-0.8	(-3.6 to 2.1)	0.60
Left ventricular end-diastolic volume (mL)	215.6	(62.5)	212.8	(60.3)	2.8	(-11.6 to 17.2)	0.70
MRI or other imaging	**(n=132)**		**(n=143)**				
Left ventricular ejection fraction (%)	45.1	(10.9)	45.1	(11.6)	0.1	(-2.7 to 2.7)	1.00
Left ventricular end-diastolic volume (mL)	209.9	(53.8)	211.5	(58.3)	-1.6	(-14.9 to 11.8)	0.82
Left ventricular end-diastolic volume index (mL/m^2)	102.9	(23.9)	104.3	(25.4)	-1.4	(-7.3 to 4.4)	0.63
Left ventricular end-systolic volume index (mL/m^2)	57.9	(22.6)	58.9	(24.8)	-1.1	(-6.7 to 4.6)	0.71
MRI only	**(n=124)**		**(n=135)**				
Left ventricular ejection fraction (%)	45.0	(10.6)	45.2	(11.5)	-0.2	(-2.9 to 2.5)	0.88
Left ventricular end-diastolic volume (mL)	213.8	(51.8)	214.8	(56.4)	-1.0	(-14.2 to 12.3)	0.89
Left ventricular end-diastolic volume index (mL/m^2)	104.9	(22.6)	105.9	(24.2)	-1.0	(-6.7 to 4.7)	0.73
Left ventricular end-systolic volume index (mL/m^2)	59.0	(22.4)	59.7	(24.5)	-0.7	(-6.5 to 5.0)	0.81
Left ventricular end-diastolic mass index (g/m^2)*	51.6	(9.2)	52.4	(12.0)	-0.8	(-3.5 to 2.0)	0.58
Dysfunctional segments (%)*	58.0	(26.6)	61.5	(27.0)	-3.6	(-10.4 to 3.2)	0.30
Total infarct size (g)†	7.6	(6.0)	7.2	(5.6)	0.4	(-1.1 to 2.0)	0.59

Data are mean ± SD. PCI=percutaneous coronary intervention. CTO=chronic total occlusion. MRI =magnetic resonance imaging.
*Data available in n=113/n=130 patients. † data available in n=95/n=114 patients.

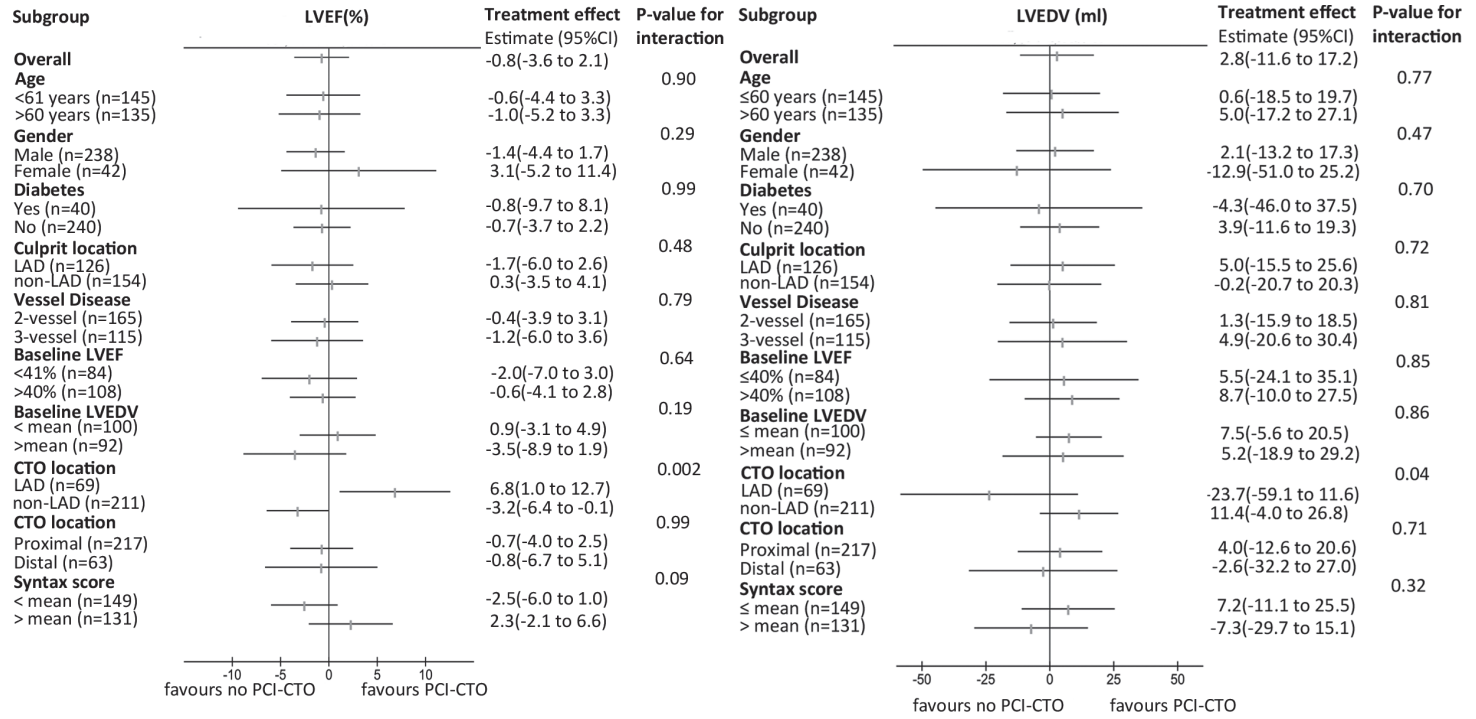

Figure 3: Forest plots of subgroup analyses for the primary outcomes.

LVEF= left ventricular ejection fraction, LVEDV= left ventricular end diastolic volume, CI= confidence interval, LAD= left anterior descending coronary artery, CTO= chronic total occlusion, PCI= percutaneous coronary intervention. * The mean LVEDV was 210.5ml, † the mean SYNTAX score was 26.5.

Table 4: Adjudicated clinical outcomes from randomization to four months follow-up.

	CTO-PCI (n=148)		No CTO-PCI (n=154)		P
Major Adverse Cardiac Events (MACE)					
Cardiac death	4	(2.7%)	0	(0%)	0.056
Myocardial infarction	5	(3.4%)	3	(1.9%)	0.49
Periprocedural†	4	(2.7%)	1	(0.6%)	-
Spontaneous/Recurrent	2	(1.4%)	2	(1.3%)	-
CABG surgery	0	-	1	(0.6%)	-
MACE*	8	(5.4%)	4	(2.6%)	0.25
Other Events					
PCI	39	(26.4%)	20	(13.0%)	0.004
CTO PCI	-	-	5	(3.2%)	-
Repeat CTO PCI	2	(1.4%)	0	(0%)	-
Non-CTO PCI in CTO vessel	10	(6.8%)	0	(0%)	0.001
Before initial CTO procedure	1	(0.7%)	-	-	-
During initial CTO procedure	9	(6.1%)	-	-	-
Post initial CTO procedure	0	-	-	-	-
PCI in non-CTO vessel	31	(20.9%)	17	(11.0%)	0.027
Before initial CTO procedure	0	(0%)	-	-	-
During initial CTO procedure	26	(17.6%)	-	-	-
Post initial CTO procedure	5	(3.4%)	-	-	-
Total stent thrombosis	5	(3.4%)	3	(1.9%)	0.49
Stent thrombosis CTO lesion	2	(1.4%)	0	(0%)	-
Definite	1	(0.7%)	0	(0%)	-
Probable	1	(0.7%)	0	(0%)	-
Timing of stent thrombosis CTO lesion					
Acute	0	(0%)	0	(0%)	-
Subacute	2	(1.4%)	0	(0%)	-
Stent thrombosis non-CTO lesion	4	(2.7%)	3	(1.9%)	0.72
Definite	3	(2.0%)	3	(1.9%)	-
Probable	1	(0.7%)	0	(0%)	-
Timing of stent thrombosis non-CTO lesion					
Acute	0	(0%)	1	(0.6%)	-
Subacute	3	(2.0%)	2	(1.3%)	-
Stroke‡	0	(0%)	2	(1.3%)	
Bleeding according to GUSTO-criteria	5	(3.4%)	2	(1.3%)	0.28
Mild	1	(0.7%)	1	(0.6%)	-
Moderate	3	(2.0%)	1	(0.6%)	-
Severe / life threatening	1	(0.7%)	0	(0%)	-

Data are number of events (%). The first event per patient is listed. PCI=percutaneous coronary intervention. CTO=chronic total occlusion. CABG=coronary artery bypass grafting. GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries. † periprocedural myocardial infarction was defined according to the third universal definition of myocardial infarction criteria *MACE is composite of Cardiac death, Myocardial infarction and CABG. ‡One patient perished from fatal stroke, there were no other non-cardiac deaths.

Clinical events

Clinical follow-up at 4 months was complete in all patients and is presented in table 4. At 4 months MACE rates were 5.4% in the CTO-PCI arm vs. 2.6 % in the No CTO-PCI arm, p=0.25 (figure 4). Repeat CTO-PCI occurred in only 2 patients in the CTO-PCI arm (1.4%). A total of five patients in the No CTO-PCI arm underwent clinically driven CTO-PCI before the 4-month endpoint. There was a higher rate of additional revascularization in non-CTO vessels in the CTO-PCI arm (20.9% vs. 11.0%, p=0.03). Definite or probable stent thrombosis occurred in 5 patients in the CTO PCI arm compared with 3 in the No-CTO PCI arm (3.4% vs. 1.9%, p=0.49). Two cases of stent thrombosis in the CTO-PCI arm were related to the treated CTO lesion: One case of angiographically confirmed definite stent thrombosis in the CTO lesion occurring 8 days after the CTO-PCI, and one case of probable stent thrombosis in one patient who died after hospital discharge on day 7 after CTO-PCI. The other three definite stent thrombosis cases in the CTO-PCI arm were definitely related to the culprit lesion of the STEMI.

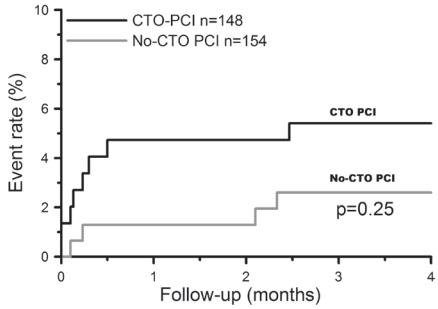

Figure 4: Major adverse cardiac events event rates at four month follow-up.
Major adverse cardiac events were composed of cardiac death, myocardial infarction and coronary artery bypass graft surgery. CTO= chronic total occlusion, PCI= percutaneous coronary intervention.

DISCUSSION

EXPLORE was the first randomized clinical trial investigating the impact of CTO-PCI on functional and clinical outcome. The EXPLORE trial showed that routine CTO-PCI did not result in higher LVEF and lower LVEDV at 4 months when compared with a No CTO-PCI strategy in an unselected cohort of STEMI patients with a concurrent CTO. We found similar MACE rates in the two treatment groups. Periprocedural MI (third universal definition) occurred in only 4 patients. There were no periprocedural deaths or emergency CABG surgeries. A subgroup analysis showed that CTO-PCI in patients with a concurrent CTO in the LAD was associated with a significantly higher LVEF after 4 months compared

with no CTO-PCI (47.2±12.3% vs. 40.4±11.9%, p=0.02), suggesting that CTO-PCI can still improve outcomes in high-risk patients. In order to be able to make any firm conclusion on this topic, further research is needed.

The CTOs were mostly located in the RCA in agreement with large registries.(19,20) The mean J-CTO score of 2±1 in EXPLORE is comparable to the mean J-CTO score in a contemporary registry study of CTO-PCI in stable coronary artery disease patients, illustrating the complexity of the patients enrolled.(21) The study protocol did not mandate usage of a specific protocol or technique for CTO-PCI, but left the technical approach to CTO-PCI at the discretion of the operator which resulted in the usage of various techniques as shown in table 2. The Investigator reported procedural success rate of 77% was similar to success rates from large CTO registry studies.(22,23). The strict corelab-adjudicated success rate of 73% was slightly lower.

Recently, the PRAMI, CULPRIT, and PRIMULTI trials studied the value of additional PCI of other flow limiting stenosis after primary PCI for STEMI. It must be borne in mind that all three studies excluded patients with concurrent CTOs.(24-26) The presence of a CTO resulted in a higher degree of complex coronary artery disease in the study cohort. In EXPLORE, 43% of patients had triple vessel disease despite the use of a strict definition (luminal stenosis >70%). This was higher than in the PRAMI, the CULPRIT and the PRIMULTI trials.(24-26) In the CULPRIT study, 23% of all patients had 3-vessel disease.(25) In the PRAMI and PRIMULTI studies MVD was defined as a luminal stenosis >50% and 3-vessel disease was reported in 36% and 31% of the 465- and 627-patient cohorts, respectively.(24,26) In EXPLORE, extent of coronary artery disease, including a concurrent CTO and expressed in an overall high SYNTAX score, also resulted in a lower baseline LVEF (41%) compared with the CULPRIT (45%) and PRIMULTI (50%) studies (baseline LVEF was not reported in the PRAMI study).

The body of evidence of a potential benefit of CTO recanalization has been derived from retrospective analyses and greatly focused on differences in clinical outcome between patients with failed and successful CTO PCI.(9) Studies focussing on potential improvement of left ventricular function are scarce and lack an adequate control group due to their non-randomized study designs.(10) A recent meta-analysis of observational studies in elective patients showed that successful CTO-PCI was associated with an improvement of 4.4% absolute LVEF points.(10) Subgroup analyses in EXPLORE revealed a significant interaction between the location of the CTO and randomized treatment allocation in terms of LVEF at four months; patients with a CTO located in the LAD randomized to the CTO-PCI strategy had significantly higher LVEF with a similar favourable trend for LVEDV . On the one hand, this finding in a subgroup of the study cohort should be interpreted with caution, but on the other hand the interaction terms for LVEF and LVEDV were highly significant and marginally significant, respectively. Moreover, prior

large registry studies have already reported a survival benefit after successful vs. failed CTO PCI when located in the LAD, but not in the RCA or the RCX.(27,28)

A major limitation of the current study is the fact that it was not powered to detect differences in hard clinical endpoints such as death, myocardial infarction, and stroke. Also, as in most randomized controlled trials, a selection of patients has occurred. Patients with high-risk characteristics (e.g. shock, ventricular arrhythmias, out-of-hospital resuscitation) were not suitable for inclusion in EXPLORE. Moreover, patients expected to have an indication for an ICD and patients with severe concomitant valvular disease and/or arrhythmias such as atrial fibrillation were not eligible for inclusion. The results of our study only apply to patients who are hemodynamically stable during the first week after primary PCI. Our results cannot be applied to acutely ill hemodynamically compromised patients. Further studies focusing on really high risk patients are needed.

Furthermore, there was no uniform protocol-specified technique for CTO-PCI, on the other hand this resulted in a 'real world' approach to CTO-PCI. For ethical reasons, the study was not blinded and no sham procedures were performed in the No CTO-PCI arm, on the other hand all primary endpoint analyses were performed by an independent corelab blinded to randomized treatment assignment. Finally, the CTO-PCI success rate was lower (73%) than expected (80%) which negatively affected the power of the study. However, as the LVEF and LVEDV were numerically similar in the CTO-PCI and no CTO-PCI groups, it is unlikely that an 80% success rate would have led to significant differences between both groups.

In conclusion, the EXPLORE trial showed that additional CTO-PCI within one week after primary PCI for STEMI was feasible and safe. In STEMI patients with a concurrent CTO we did not find an overall benefit for CTO-PCI in terms of LVEF or LVEDV. However, a subgroup analysis suggests that patients with a CTO in the LAD may benefit from early additional CTO-PCI.

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APPENDIX A

Inclusion criteria

Patients with a non-infarct related chronic total occlusion undergoing successful primary PCI for STEMI (within twelve hours of onset of symptoms) are screened for entry into this trial. For the purpose of this trial, a primary PCI is 'successful' when the residual stenosis of the culprit lesion < 30% and the TIMI flow ≥ 2.

STEMI is diagnosed when both of the following apply:

- Typical chest pain
- Electrocardiographic new or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in leads V_1, V_2, or V_3 and ≥ 0.1 mV in other leads.

Patients are suitable for inclusion in this trial if coronary angiography preceding the primary PCI reveals at least one chronic total occlusion with all of the following characteristics:

1. Located in a non-infarct related coronary artery:
a. In the left coronary system if the right coronary artery (RCA) is the culprit lesion
b. In the RCA or left circumflex artery (LCX) if the left anterior descending artery (LAD) is culprit lesion;
c. In the RCA or LAD if the LCX is the culprit lesion.
2. A 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels
3. Amenable to PCI treatment, as assessed by the local heart team and dedicated CTO operators
4. A reference diameter of ≥ 2.5 millimeters by visual estimation

APPENDIX B

Exclusion criteria

1. Older than 80 years of age
2. Persistent or permanent atrial fibrillation
3. Known renal insufficiency (e.g. serum creatinine level of more than 265 µmol/L (i.e. more than 3.5 mg/L))
4. More than 48 hours of hemodynamic instability after primary PCI, defined as pre-shock (heart rate >100/min. and or systolic blood pressure <100 mmHg) or shock (sustained systolic blood pressure ≤ 80 mmHg despite fluid hydration with ≥ two low dose or one high dose vasopressor or inotropic drug(s) or a cardiac index of ≤ 2.2 liters per minute per square meter of body-surface area and a pulmonary-capillary wedge pressure of at least 15 mmHg if known)
5. Cardiac events between primary PCI and randomization:

a. Extended myocardial infarction, as evidenced by a new episode of chest pain with new ST-segment elevations and a new CK / CK-MB peak
b. Acute stent thrombosis
c. Ventricular arrhythmias, i.e. sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) more than 48 hours after primary PCI (i.e. late ventricular arrhythmia)

6. Significant left main stenosis (diameter stenosis ≥ 50%)
7. Indication for Coronary Artery Bypass Grafting (CABG)
8. Severe valvular heart disease requiring cardiac surgery within four months
9. Indication for implantable cardioverter defibrillator (ICD) within four months
10. Inability to schedule the index procedure within seven days after primary PCI
11. Unsatisfactory baseline investigations, i.e. MRI not suitable for endpoint assessment
12. Any contraindication for MRI, i.e.:

a. pacemaker
b. cerebrovascular clips
c. claustrophobia

13. Serious known concomitant disease with a life expectancy of less than one year
14. Circumstances that prevent follow-up (no permanent home or address, transient, etc.)
15. Previous participation in this trial
16. Current participation in another trial

SUPPLEMENTARY DATA APPENDIX

Table 1: TIMI flow post CTO-PCI per treatment group:

TIMI flow post CTO-PCI	Successful CTO-PCI (n=108)	Not successful CTO-PCI (n= 39)
0	0	30 (76.9%)
1	0	6 (15.4%)
2	2 (1.9%)	3 (7.7%)
3	106 (98.1%)	0

Table 2: Frequency All J-CTO total scores per treatment group, and in the total group (core-lab adjudicated on pPCI angiography):

J-CTO	CTO-PCI (n=148)	No CTO-PCI (n=154)	Total (n=302)
0	11 (7.4%)	5 (3.2%)	16 (5.3%)
1	37 (25%)	33 (21.4%)	70 (23.2%)
2	45 (30.4%)	50 (32.5%)	95 (31.5%)
3	39 (26.4%)	41 (26.6%)	80 (26.5%)
4	16 (10.8%)	24 (15.6%)	40 (13.2%)
5	-	1 (0.6%)	1 (0.3%)

Table 3: Segment of the CTO per treatment group, and in the total group (core-lab adjudicated):

CTO segment	CTO-PCI (n=148)	No CTO-PCI (n=154)	Total (n=302)
1 RCA-prox	18 (12.2%)	20 (13%)	38 (12.6%)
2 RCA-mid	38 (25.7%)	45 (29.2%)	83 (27.5%)
3 RCA-dist	8 (5.4%)	12 (7.8)	20 (6.6%)
4 RDP	0	1 (0.6%)	1 (0.3%)
5 LM	0	0	0
6 LAD-prox	4 (2.7%)	14 (9.1%)	18 (6.0%)
7 LAD-mid	30 (20.3%)	17 (11%)	47 (15.6%)
8 LAD-dist	0	4 (2.6%)	4 (1.3%)
9 D1	2 (1.4%)	4 (2.6%)	6 (2.0%)
10 D2	0	0	0
11 RCx-prox	15 (10.1%)	8 (5.2%)	23 (7.6%)
12 OM1/IM	8 (5.4%)	7 (4.5%)	15 (5.0%)
13 RCx-dist	19 (12.8%)	18 (11.7%)	37 (12.3%)
14 OM2	6 (4.1%)	4 (2.6%)	10 (3.3%)
15 LDP	0	0	0
16 RPL	0	0	0

APPENDIX C

Power calculation considerations

The power calculation for the EXPLORE trial resulted from a process where all evidence available at the time of the inception of the trial (2006) was weighed. It would have been impossible to provide an entirely accurate power calculation as EXPLORE is the first trial of its kind. However, in our own cohort of patients receiving successful CTO-PCI we had found a mean LVEF of approximately 40%. Moreover, a meta-analysis performed at that time (which was eventually published in an updated form in 2015) showed a mean difference of 4.81% in LVEF in favor of patients receiving CTO-PCI compared to patients not receiving CTO-PCI (Chung et al, Danchin et al, Dzavik et al, Engelstein et al, Ermis et al, Fang et al, Gottschall et al, Heyder et al, Ivanhoe et al, Jin et al, Kux et al, Melchior et al, Mori et al, Piscione et al 2005, Schacherer et al, Sirned et al, Werner et al). This was rounded off to a 5% expected difference of LVEF. Since we estimated a success rate of 80%, this resulted in an absolute difference of 4% (leading to the expected LVEF of 36% in the conservative group).

Regarding the power calculation for LVEDV, the calculations were based on all available data available in 2006 (Danchin et al, Fang et al, Piscione et al, Baks et al). In these studies, a mean difference in LVEDV index of -6.5ml/m2 was found after CTO-PCI. In EXPLORE absolute LVEDV values were used instead of LVEDV index; assuming a mean body surface area of 1.9m2 in men this resulted in an absolute reduction of 12.35ml. This number was rounded to 15ml and used this for the calculation. As mean baseline LVEDV we used the values of patients with an ejection fraction around 40% (which was 200ml).

Chapter 14

Summary

Concluding remarks and future perspectives

SUMMARY OF THE THESIS

Ever since it was possible to view the status of the coronary arteries through angiography in 1958, it is known that mortality increases with the severity and extent of coronary artery disease (CAD). Multivessel disease (MVD) is present in more than half of the patients with CAD and a chronic total occlusion (CTO) is present in approximately 16%. In patients with stable CAD, percutaneous coronary intervention (PCI) upon optimal medical treatment is mainly performed for symptom relieve only rather than improvement of prognosis which is different in the setting of acute myocardial infarction. Primary PCI upon medical therapy in the setting of ST-elevation myocardial infarction has been shown to significantly decrease morbidity and mortality. However, mortality rates after primary PCI is still high in several high risk subgroups. In 2006, our research group discovered that the increased mortality rate observed in patients with STEMI and MVD, was merely due to the presence of a CTO in a non-infarct related artery (IRA). After stratification of the MVD-patients into patients with and without a CTO in a non-IRA, patients with MVD without a CTO had a comparable mortality rate to patients with single vessel disease (SVD) whereas the mortality rate of STEMI patients with a CTO was three-fold higher compared to patients with SVD and MVD without a CTO. The thesis presented here elaborates on this initial finding. In **chapter 2**, we describe the current available literature regarding CTO definition, histology, patient characteristics, evidence of treatment, advice for clinical decision making and future perspectives. In **chapter 3**, we used the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR) database to investigate characteristics of CTO patients and procedures. The study population consisted of all consecutive patients who underwent coronary angiography in Sweden between January 1th 2005 and January 1th 2012. 276,931 procedures (coronary angiography or PCI) were performed in 215,836 patients registered in SCAAR. Registry data were scrutinized for the presence of CTO, which was defined as 100% luminal diameter stenosis known or assumed to be ≥3 months old. After exclusion of patients with previous coronary artery bypass graft (CABG) surgery or coronary occlusions due to acute coronary syndrome, we identified 16,818 CTO patients. We found that a CTO was observed in 10.9% of all coronary angiographies and in 16.0% of patients with CAD. The majority of CTO patients were treated conservatively and PCI of CTO accounted for only 5.8% of all PCI procedures. The low percentage reflects the difficulty of the procedure but also the lack of randomized evidence proving its benefit. CTO patients with diabetes and MVD were more likely to be referred to CABG. We determined the prognostic impact of a CTO in the whole SCAAR cohort in **Chapter 4**. We compared the long-term mortality rates of patients with and without a CTO and tested for interactions between CTO and several prespecified characteristics such as indication for angiography and PCI, severity of CAD, age, gender, and diabetes. During the study period, 14,441 CTO and 75,431

non-CTO patients were registered in SCAAR. The presence of a CTO was associated with higher mortality. In subgroup analyses, mortality risk was lowest in patients with stable angina and highest in those with STEMI. In addition, CTO was associated with highest risk in patients under 60 years of age and lowest risk in octogenarians. There was no interaction between CTO and either diabetes or gender, suggesting an equally adverse effect in both groups.

Part II of this thesis concerns CTO patients with stable CAD. In **chapter 5**, we present the results from the large Multinational CTO Registry in patients with stable CAD, which is a combined effort from the San Raffaele Scientific Institute in Milan, Italy, Asan Medical Center in Seoul, South Korea, and Colombia University Medical Center, New York, USA. Patients were included between 1998 and 2007. A total of 1791 consecutive patients with 1852 CTOs underwent PCI. We investigated if procedural success rates and long-term clinical outcome of CTO-PCI in elderly patients ≥75 years differ compared to younger patients. Outcomes included procedural success and major adverse cardiac events, a composite of mortality, myocardial infarction or coronary artery bypass graft surgery (CABG). 213 patients (12%) were aged ≥75 years. Procedural success rates were similar in elderly patients compared with patients <75 years. MACE rates after successful vs. failed PCI were 25.8% vs. 42.3% in the elderly (p=0.02) and 11.2 vs. 20.8% in younger patients (p<0.01). In elderly patients, this reduction in MACE after successful PCI was mainly driven by a reduction in CABG as there were no significant differences in terms of mortality or MI. In conclusion, CTO PCI in patients ≥75 years has similar success as in patients <75 years. In elderly patients undergoing CTO PCI, MACE rates were relatively high but successful revascularization is associated with a reduction in MACE at 5-year follow-up in both elderly and younger patients. In CTO patients with stable CAD all available evidence on outcome data are from observational studies with often small cohort sizes. Therefore in **chapter 6** we performed a meta-analyses on the outcomes left ventricular function and long-term mortality. Of the 812 citations, 34 studies performed between 1987-2014 in 2,243 patients were eligible for LVEF and 27 studies performed between 1990-2013 in 11,085 patients with successful and 4,347 patients with failed CTO PCI were eligible for long-term mortality. After successful CTO PCI, LVEF increased with 4.44% compared to baseline. In a small cohort of ~70 patients, no significant difference in LVEF was observed after non-successful CTO PCI or reocclusion. Additionally, 8 studies reported the change in left ventricular end-diastolic volume (LVEDV) in a total of 412 patients where LVEDV decreased with 6.14 ml/m^2. Successful CTO PCI was also associated with reduced long-term mortality in comparison with failed CTO PCI (odds ratio (OR): 0.52.

Part III concerns STEMI patients with a CTO in a non-IRA. In **chapter 7 and 8**, we return to the AMC primary PCI cohort where we investigated the prognostic impact of a MVD with and without a CTO in several subgroups. **Chapter 7** investigated patients with and without diabetes mellitus (DM). Between 1997 and 2007 we treated 4506 STEMI patients

with primary PCI of whom 539 (12%) had a confirmed diagnosis of DM at admission. STEMI patients with DM more often had MVD, both with and without a CTO in a non-IRA compared with non-diabetic STEMI patients. MVD with a CTO was an independent predictor of 5-year mortality in DM and non-DM patients, whereas MVD without a CTO was not. **Chapter 8** studied the impact of a MVD with and without a CTO stratified according to cardiogenic shock (CS). From January 1997 through December 2008 a total of 4409 (88%) STEMI patients presented without CS and 609 patients (12%) presented with CS. In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, MVD with and without a CTO were predictors for short term mortality. STEMI patients with a CTO have a worse prognosis than STEMI patients without a CTO but in **Chapter 9** we investigated whether there was a differential prognostic effect according to the location of the IRA and CTO-lesion. From January 2000 through December 2012, there were a total of 480 STEMI patients with a CTO in a non-IRA treated with primary PCI in our hospital of whom the diagnostic angiography was available. STEMI CTO patients with the CTO artery in the proximal LAD or the culprit artery in the LAD or proximal LCX constitute the subgroup with the highest risk of mortality. Throughout the thesis we speculate about the possibility that prognosis may be improved upon CTO revascularization while PCI of nonCTO lesions in other vessels than the culprit artery appear to have no effect, **chapter 10** and **11. Chapter 12** describes the study design of the first randomized clinical trial in the field of CTO PCI, namely: Evaluating Xience V and Left Ventricular Function in PCI on Occlusions in STEMI (EXPLORE) trial. In total, 300 STEMI patients with a CTO in a non-IRA were randomized 1:1 to either PCI of the CTO within 1 week after the PPCI procedure upon optimal medical treatment compared to optimal medical treatment alone. The primary endpoints are left ventricular ejection fraction and left ventricular end-diastolic volume measured on Magnetic Resonance Imaging four months after the index event. Clinical follow-up will continue up to 5 years. In the final chapter, **chapter 13,** we report the outcome of the EXPLORE trial. The trial showed that routine CTO-PCI did not result in higher LVEF and lower LVEDV at 4 months when compared with a No CTO-PCI strategy in an unselected cohort of STEMI patients with a concurrent CTO. However, a subgroup analysis showed that CTO-PCI in patients with a concurrent CTO in the LAD was associated with a significantly higher LVEF after 4 months compared with No CTO-PCI (47.2±12.3% vs. 40.4±11.9%, p=0.02). This finding warrants further investigation.

SAMENVATTING VAN HET PROEFSCHRIFT

De bevindingen van het coronair angiogram spelen een grote rol ten aanzien van de klinische beslissing om wel of niet invasief te behandelen naast optimale medicamenteuze therapie, zoals percutane coronair interventie (PCI) danwel coronaire bypass operatie. Om deze reden is het noodzakelijk de bevindingen op het angiogram te correleren aan prognose, alvorens een eventueel therapie te evalueren. Sinds de komst van het angiogram in 1958 is het bekend dat de mortaliteit stijgt naar mate de ernst en uitgebreidheid van het coronarialijden toeneemt. Meervatslijden is in meer dan de helft van de patiënten met coronarialijden aanwezig en van deze patiënten heeft ongeveer 16% een chronische totale occlusie (CTO). Bij patiënten met stabiel coronarialijden zal PCI naast optimale medicamenteuze behandeling alleen helpen voor de klachten van de patiënt echter zal het geen effect hebben op de prognose. Dit is wel het geval bij een acuut myocard infarct met ST-segment elevatie op het elektrocardiogram. Hoewel het direct dotteren, primaire PCI, ten opzichte van trombolyse voor een acuut myocard infarct een gunstig effect heeft op morbiditeit en overleving, is de mortaliteitspercentage in bepaalde risicogroepen nog steeds erg hoog. In 2006 heeft onze studiegroep ontdekt dat de verhoogde mortaliteit gezien in ST-elevatie myocard infarct (STEMI) patiënten met meervatslijden ten opzichte van eenvatslijden, bijna geheel te wijten is aan de aanwezigheid van een CTO in een non-infarct gerelateerde arterie (IRA). Deze bevinding staat ten grondslag aan dit proefschrift waar we dit verder proberen te specificeren. In **hoofdstuk 2** beschrijven we de huidige beschikbare literatuur over CTO definities, histologie, patiënt karakteristieken, bewijs voor behandeling, advies ten aanzien van besluit om wel of niet te behandelen en een vooruitblik naar de toekomst. In **hoofdstuk 3** beschrijven we de CTO prevalentie, patiënt en procedure karakteristieken uit de nationale Swedish Coronary Angiography and Angioplasty Registry (SCAAR) database. De studiepopulatie bestaat uit alle patiënten die tussen januari 2005 en 2012 een coronair angiogram dan wel PCI hebben ondergaan. In totaal waren er 276,931 procedures verricht in 215,836 patiënten. Van deze patiënten werd bepaald of er een CTO aanwezig was waarbij patiënten die in het verleden coronaire bypass chirurgie hadden ondergaan of waarbij de coronaire occlusie mogelijk acuut was in het kader van een myocard infarct, werden geëxcludeerd. In totaal werden er 16,818 CTO patiënten geïdentificeerd. Een CTO was aanwezig in 10.9% van alle coronair angiogrammen die werden vervaardigd waarbij dit percentage toenam naar 16% bij patiënten met significant coronarialijden. De meerderheid van de patiënten werd conservatief behandeld. Van alle PCI procedures, betrof het in 5.8% van de gevallen een CTO procedure. Dit lage percentage reflecteert deels de moeilijkheid van de procedure maar ook het gebrek aan gerandomiseerde data ten aanzien van het voordeel van CTO PCI. CTO patiënten met diabetes mellitus en meervatslijden hadden meer kans om behandeld te worden met

coronaire bypass chirurgie. In **hoofdstuk 4** hebben we de prognostische impact van een CTO in de gehele SCAAR database onderzocht waarbij we de mortaliteitspercentages op de langere termijn hebben vergeleken tussen patiënten met en zonder CTO. Daarnaast hebben we verschillende interacties getest tussen de aanwezigheid van een CTO en enkele voorop vastgestelde subgroepen zoals de indicatie voor de angio/PCI procedure, ernst van coronarialijden, leeftijd, geslacht en diabetes mellitus. Tijdens de studieperiode hadden 14,441 patiënten een CTO en 75,431 geen CTO. Het hebben van een CTO was geassocieerd met een hogere mortaliteit. Het mortaliteitsrisico was het laagst bij patiënten met stabiel coronarialijden waarbij het risico toenam naarmate de indicatie voor de procedure ernstiger werd, met dus het hoogste risico in de STEMI subgroep. Daarnaast was het hebben van een CTO geassocieerd met een hogere mortaliteit bij patiënten <60 jaar en het laagst bij patiënten ≥80 jaar. Er was geen associatie tussen de aanwezigheid van een CTO en de subgroepen diabetes mellitus (DM) of geslacht, wat suggereert dat ongeacht de aanwezigheid van een CTO, het risico op overlijden niet verandert in zowel patiënten met als zonder diabetes en zowel mannen als vrouwen.

Het tweede gedeelte van het proefschrift betreft onderzoek naar patiënten met stabiel coronarialijden. In **hoofdstuk 5** presenteren we de resultaten van een grote multinationale CTO database van patiënten met stabiel coronarialijden. De participerende ziekenhuizen zijn San Raffaele Scientific Institute in Milaan, Italië, Asan Medical Center in Seoul, Zuid-Korea en Colombia University Medical Center, New York, VS. In totaal werden er 1.791 patiënten geïncludeerd die een CTO procedure ondergingen tussen 1998-2007. In dit cohort, hebben we onderzocht of de procedurele succes kans en prognose verschillend waren in oudere patiënten ≥75 jaar (n=213, 12%) ten opzichte van patiënten <75 jaar. Het eindpunt prognose bestond uit een samengesteld eindpunt namelijk: major adverse cardiac events (MACE) bestaande uit mortaliteit, myocard infarct en coronaire bypass chirurgie. De procedurele succespercentages waren gelijk in beide leeftijdsgroepen. Het percentage MACE na een succesvolle versus niet succesvolle CTO PCI was veel hoger in de oudere patiënten (25,8% versus 42.3%, p=0.02) ten opzichte van de jongere patiënten (11.2 vs. 20.8%, p<0.01). Het verschil in MACE bij de oudere patiënten werd met name bepaald door het verschil in bypass chirurgie. Concluderend, CTO PCI in patiënten ≥75 jaar hebben vergelijkbare succespercentages als patiënten <75 jaar. In oudere patiënten zijn de MACE percentages relatief hoog echter is succesvolle CTO revascularisatie geassocieerd met een afname in MACE gedurende 5 jaar follow-up in zowel de oudere als de jongere groep. In CTO patiënten met stabiel coronarialijden, is er nog geen gerandomiseerde data beschikbaar. Alle literatuur is afkomstig van observationele studies met vaak kleine cohorten. Om deze reden hebben we in **hoofdstuk 6** een meta-analyse gedaan naar de uitkomst van LVF en de mortaliteit op de langere termijn. Van de 812 citaties, waren er 34 studies geschikt voor de uitkomst LVF met in totaal 2.243 patiënten. In totaal waren er 37 studies geschikt voor de uitkomst mortaliteit in 11.085

patiënten met een succesvolle CTO PCI en 4.347 met een niet succesvolle CTO PCI. Na een succesvolle CTO PCI, nam de LVF met 4,44% toe in vergelijking met voor de procedure. In een klein cohort van ~70 patiënten werd er geen verschil in LVF geobserveerd na een niet succesvolle CTO PCI of na reocclusie. In totaal rapporteerde 8 studies het verschil in LVEDV na een succesvolle CTO PCI waarbij de LVEDV met 6,14 ml/m^2 afnam. Daarnaast bleek een succesvolle CTO PCI geassocieerd met een betere overleving ten opzichte van een niet succesvolle procedure (odds ratio (OR): 0.52).

Het derde gedeelte betreft onderzoek naar STEMI patiënten met een CTO in een non-IRA. In hoofdstuk 7 en 8 beschrijven we de impact van een CTO in verschillende STEMI subgroepen van het primaire PCI cohort van het academisch medisch centrum (AMC). **Hoofdstuk 7** onderzoekt patiënten met en zonder DM. Tussen 1997 en 2007 zijn er in totaal 4506 STEMI patiënten behandeld met primaire PCI van wie er 539 (12%) bij opname bekend waren met DM. STEMI patiënten met DM hadden vaker meervatslijden en vaker een CTO in een non-IRA in vergelijking met niet DM patiënten. De aanwezigheid van een CTO in een non-IRA was een onafhankelijke voorspeller voor mortaliteit in zowel patiënten met DM als zonder DM terwijl meervatslijden zonder CTO dat niet was. **Hoofdstuk 8** onderzoekt de impact van meervatslijden met en zonder CTO in patiënten met en zonder cardiogene shock (CS). Tussen 1997-2008 waren er in totaal 4409 (88%) STEMI patiënten zonder CS en 609 (12%) STEMI patiënten met CS. In patiënten zonder CS werd zowel de korte als langere termijnsmortaliteit met name bepaald door de aanwezigheid van meervatslijden met een CTO en niet door meervatslijden zonder CTO. In patiënten met CS zijn zowel meervatslijden zonder als met CTO voorspellers voor de mortaliteit op korte termijn. We weten nu dat STEMI patiënten met meervatlijden met een CTO een slechtere prognose hebben dan patiënten met meervatslijden zonder CTO. In **hoofdstuk 9** hebben we onderzocht of de lokalisatie van de CTO en de culprit lesie de prognose nog verder beïnvloedt. Tussen januari 2000 t/m december 2012 waren er van 480 STEMI patiënten met een CTO in een niet infarct gerelateerde coronair arterie het diagnostische angiogram beschikbaar. In deze groep bleek dat patiënten met de CTO in de proximale LAD of de culprit lesie in de LAD of proximale RCX het grootste risico lopen om te overlijden. Gedurende het proefschrift speculeren we of CTO revascularisatie de prognose zou kunnen verbeteren terwijl gebleken is dat PCI van nonCTO lesies in andere kransslagvaten dan de culprit arterie geen effect liet zien (**hoofdstuk 10** en **11)**. In **hoofdstuk 12** beschrijven we het design van de eerste gerandomiseerde klinische studie op het gebied van behandeling van CTO in STEMI patiënten, namelijk Evaluating Xience V and Left Ventricular Function in PCI on Occlusions in STEMI (EXPLORE) studie. In totaal worden er 300 STEMI patiënten met een CTO in een non-IRA gerandomiseerd 1:1 naar PCI van de CTO binnen een week na de primaire PCI procedure bovenop optimale medicamenteuze therapie versus alleen optimale medicamenteuze therapie. De primaire eindpunten zijn linker ventrikel functie (LVF) en eind-diastolisch volume van

het linker ventrikel (LVEDV), gemeten met een Magnetic Resonance Imaging (MRI) scan na 4 maanden follow-up. De totale klinische follow-up is 5 jaar.

In **hoofdstuk 13** beschrijven we de resultaten van de EXPLORE studie. De studie liet zien dat routine CTO-PCI niet resulteerde in een hogere LVEF dan wel lagere LVEDV op 4 maanden ten opzichte van de groep waarbij geen CTO-PCI was uitgevoerd. In een subgroup van patiënten met een CTO in de LAD bleek routine CTO-PCI wel een gunstig effect te hebben op de LVEF (47.2±12.3% vs. 40.4±11.9%, p=0.02). Deze bevinding zal verder onderzocht moeten worden.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

This thesis describes that a chronic total occlusion (CTO) is a common finding on diagnostic coronary angiography. Patients with a CTO have a worse clinical outcome compared with patients without a CTO. Patients with a CTO have a worse left ventricular function and a higher mortality rate, regardless of age, gender, indication for angiography, location, hemodynamic, or diabetic status. Approximately 10% of patients with an acute ST segment myocardial infarction (STEMI) also exhibit a CTO. Patients with STEMI and a CTO, especially when located in the proximal left anterior descending coronary artery (LAD) are at even higher risk for adverse clinical outcome.

Throughout the thesis, the main following question remains: ''is a CTO just a marker of worse prognosis or is it a modifiable marker with, when successfully revascularized by percutaneous coronary intervention (PCI), yielding improved clinical outcome". The meta-analysis performed in patients with stable coronary artery disease and a CTO showed that successful versus failed CTO PCI is related with an absolute increase of 4.4% left ventricular ejection fraction points. Almost every paper in this thesis ends with the concluding remark that ''randomized controlled trials are needed to address this "open CTO" hypothesis. The EXPLORE trial was the first study to address this question in STEMI patients with a CTO in a non-infarct related artery." Although revascularization of the CTO early after STEMI treatment appeared to be safe, the trial did not show a beneficial effect on left ventricular function. However, a significant effect was present in a subgroup of CTO patients with the CTO in the LAD. Although the short term results did not support a routine strategy of opening the CTO in the first week after STEMI in all patients, many questions remain. Left ventricular remodeling and recovery are complex processes that are not complete after 4 months. As the hypothesis of CTO revascularization is based on the restoration of the contractile function of the hibernating myocardium, but also on the improvement of the healing of the infarct border zone, one can imagine that with increasing extent of hibernation or with increasing extent of myocardial infarction, the expected beneficial effect of revascularization would be larger and may take more time than 4 months. Additionally, the expected pathophysiological effect of the hypothesis of CTO revascularization would be more pronounced in LAD CTOs as the importance of the anterior wall of the left ventricle on prognosis and left ventricular function has been well documented in both stable coronary artery disease as in patients with acute myocardial infarction. As our goal was to include a real world population we also included smaller sized vessels, for example, a CTO of a non-dominant RCA or a diagonal branch while a more proximal or LAD location with a larger CTO area and thus more hibernating myocardium would augment the expected positive effect of revascularization. Another yet unaddressed issue is the potential effects of collateral circulation between the culprit artery and CTO. When the underlying myocardium of the CTO is perfused through col-

lateral circulation it's perfusion could be endangered when the donor artery is blocked in case of STEMI resulting in a more extensive infarcted area. Other issues such as index infarct size or timing of the CTO PCI may also have an effect on LV function. Subgroup analyses and long term MRI data on left ventricular function will shed additional light on these matters.

Several other comments concerning the study design can be addressed which could have contributed to the observed neutral effect. Explore included non-cardiogenic shock patients while previously our research had shown that in patients with cardiogenic shock multivessel disease with and without a CTO were both associated with reduced LVEF and increased mortality which was more severe compared to non-cardiogenic shock patients. Patients in cardiogenic shock have reduced cardiac output and coronary blood flow which may increase the functional importance of non-occlusive MVD lesions, resulting in myocardial ischemia in other perfusion areas than that of the culprit lesion. Interestingly, in non-shock patients only multivessel disease with a coexisting CTO was associated with reduced left ventricular function. For this reason, in this very ill patient population, revascularization of the CTO with perhaps even complete revascularization could significantly improve prognosis but is in the majority of cases not feasible due to the long procedure time.

In the EXPLORE trial, left ventricular function at baseline was reasonably well and therefore the expected improvement would be less than in a subgroup with poor ventricular function. Another possible explanation for the neutral effect concerns the imaging protocol which measures left ventricular function in rest while myocardial contraction in the CTO region at rest may be normal due to sufficient collateral circulation but upon exercise ischemia exist in the majority of cases which might show a reduced left ventricular function upon a stress MRI compared to patients with a revascularized CTO.

Future studies are needed to address if CTO revascularization within these subgroups could be beneficial, not only in STEMI patients but also in non-STE ACS and stable CAD patients. However, as the inclusion period of the first randomized trial, EXPLORE, took over 7 years with 14 participating centers, initiating a future trial will be quite challenging.

Currently, two randomized trials are enrolling patients with CTO and stable CAD which could shed more light into the ''CTO darkness''. The EuroCTO trial will randomly assign 1,200 patients with stable angina to either PCI and optimal medical therapy or optimal medical therapy only. The primary end point is quality of life at 1 year and major cardiovascular events (a composite of all-cause death and nonfatal myocardial infarction) at 3 years. Similarly, investigators in the DECISION-CTO trial will randomly assign 1,284 patients with stable angina (in a 1:1 ratio) to PCI and optimal medical therapy or optimal

medical therapy only. The primary end point being a composite of all-cause mortality, myocardial infarction, stroke, and any revascularization at 3-year follow-up.

Opening a CTO: work in progress.

AFSLUITENDE OPMERKINGEN EN TOEKOMSTIGE ONTWIKKELINGEN

Uit dit proefschrift is naar voren gekomen dat een chronische totale occlusie (CTO) frequent op een angiogram wordt geobserveerd en dat deze patiënten een slechtere prognose hebben in vergelijking met patiënten zonder een CTO wat betreft onder andere linker ventrikel functie en mortaliteit. Deze observatie staat los van leeftijd, geslacht, indicatie voor het angiogram, locatie van de CTO, hemodynamiek en aanwezigheid van diabetes mellitus. Ongeveer 10% van de patiënten met een acuut ST-segment elevatie myocardinfarct (STEMI) hebben ook een CTO. Patiënten met een STEMI en een CTO, met name wanneer deze in de linker anterior descending arterie (LAD) gelokaliseerd is, hebben een nog slechtere prognose. Gedurende het gehele proefschrift komt er steeds 1 vraag naar voren: ''is de aanwezigheid van een CTO alleen een kenmerk van een slechtere prognose of kan deze prognose worden verbeterd door percutane coronair interventie (PCI)." De meta-analyse verricht in dit proefschrift in CTO patiënten met stabiel coronair lijden, liet zien dat een succesvolle CTO behandeling de linker ventrikel functie met 4.4% ejectie fractie punten liet verbeteren ten opzichte van patiënten die geen succesvolle CTO behandeling hadden ondergaan. Bijna elk artikel in dit proefschrift eindigt met de concluderende opmerking dat gerandomiseerde studies nodig zijn om de ''open CTO" hypothese te onderzoeken. De EXPLORE studie was de eerste studie die deze vraag onderzocht in STEMI patiënten met een CTO in een niet infarct gerelateerde coronair arterie. Alhoewel de EXPLORE studie veilig bleek te zijn, liet de studie geen voordeel zien van percutane CTO revascularisatie wat betreft verbetering van linker ventrikel functie. Er was echter wel een significant effect aanwezig in de LAD subgroep betreffende de CTO locatie. Alhoewel de korte termijn resultaten routine opening van CTO lesies gedurende de eerste week na STEMI niet ondersteunt, blijven veel vragen nog onbeantwoord. Remodeling en herstel van het linker ventrikel zijn complexe processen die na 4 maanden nog niet voltooid zijn. Aangezien de hypothese van CTO revascularisatie is gebaseerd op de verbetering van de contractiele functie van het hibernerende myocard maar ook de verbetering van de genezing in de aangrenzende randgebieden van de infarct zone, kan men zich voorstellen dat des te uitgebreider het gebied van hibernatie en infarct zone is, des te groter het verwachte positieve effect zal zijn na revascularisatie echter zal dit mogelijk langer duren dan 4 maanden. Daarnaast zal het verwachte pathofysiologische effect van de ''open CTO" hypothese groter zijn in LAD CTOs aangezien de bijdrage van de anterieure zijde van het linker ventrikel aan de ventrikel functie en prognose in eerdere literatuur al is bewezen in zowel patiënten met stabiel coronair lijden als in patiënten met een myocard infarct.

Ons streven was om de dagelijkse praktijk na te bootsen. Om deze reden hebben wij ook CTOs in kleinere coronair vaten geaccepteerd, zoals een CTO van een niet dominante RCA of een CTO in een diagonaal arterie terwijl een meer proximale locatie

of een LAD locatie met een groter CTO gebied en dus meer hibernerend myocard het verwachte effect van revascularisatie veel groter zou zijn.

Daarnaast zal het effect van een collaterale circulatie tussen de culprit arterie en de CTO verder onderzocht moeten worden. Wanneer het CTO myocard qua bloedvoorziening afhankelijk is van collateralen vanuit de culprit arterie, zal ten gevolge van een acute blokkade, resulteren in een veel groter infarctgebied. Andere variabelen zoals de index infarct grootte of de timing van de CTO procedure kunnen ook een effect hebben op de linker ventrikel functie. Subgroep analyses en MRI data op langere termijn zullen hier meer helderheid over kunnen verschaffen.

Enkele andere opmerkingen over het studie ontwerp kunnen worden aangehaald welke mogelijk hebben bijgedragen aan het geobserveerde neutrale effect. In de EXPLORE studie werden alleen patiënten geïncludeerd zonder cardiogene shock terwijl eerder onderzoek door onze groep heeft laten zien dat patiënten met cardiogene shock een sterk verminderde linker ventrikel functie hadden en een hogere mortaliteit in zowel de groep met meervatslijden zonder CTO als met CTO welke in ernstigere mate aanwezig waren in vergelijking met patiënten zonder cardiogene shock. Patiënten in cardiogene shock hebben een verminderde cardiogene output en verminderde coronaire bloeddoorstroming waardoor het obstruerende effect van een niet occlusieve lesie toeneemt waardoor ook in andere gebieden dan de culprit arterie ischemie kan ontstaan. In patiënten zonder cardiogene shock, was meervatslijden zonder CTO geen voorspeller voor verminderde linker ventrikel functie of mortaliteit. Om deze reden zou in deze zieke patiëntenpopulatie, revascularisatie van de CTO en zelfs complete revascularisatie de prognose sterk kunnen verbeteren echter is dit meestal niet haalbaar door de lange procedure tijd.

In de EXPLORE studie was de linker ventrikel functie op baseline redelijk goed waardoor de verwachte verbetering minder groot zal zijn dan in een subgroep met een slechte linker ventrikel functie.

Een andere verklaring voor het neutrale effect betreft het MRI protocol waarbij de linker ventrikel functie werd bepaald in rust terwijl de myocardiale contractie in het CTO gebied in rust normaal kan zijn door voldoende perfusie middels collaterale circulatie. Gedurende inspanning schiet deze collaterale circulatie in meer dan 90% van de patiënten tekort waardoor er op dat moment ischemie en verminderde contractie kan ontstaan in vergelijking met patiënten waarvan de CTO geopend is.

Toekomstige studies moeten uitwijzen of CTO revascularisatie in deze subgroepen effectief zal zijn zowel in STEMI patiënten als patiënten met non-ST elevatie myocard infarct, acuut coronair syndroom en stabiel coronair lijden, echter aangezien de inclusie periode van de eerste gerandomiseerde studie, EXPLORE, meer dan zeven jaar heeft geduurd met 14 internationale centra, zal het organiseren van een toekomstige studie zeer uitdagend zijn.

Op dit moment lopen er nog twee gerandomiseerde studies in CTO patiënten met stabiel coronair lijden welke meer duidelijkheid kunnen geven. De EuroCTO trial zal 1200 patiënten randomiseren tussen optimale medicamenteuze therapie met PCI versus medicamenteuze therapie alleen. Het primaire eindpunt is kwaliteit van leven op 1 jaar en majeure cardiovasculaire adverse events (samengesteld eindpunt: dood en niet fataal myocard infarct) op 3 jaar.

Een vergelijkbare studie is de DECISION-CTO studie welke 1284 patiënten randomiseren naar optimale medicamenteuze therapie met versus zonder PCI. Het primaire eindpunt is een samengesteld eindpunt bestaande uit dood, myocard infarct, cerebro vasculair accident en elke toekomstige revascularisatie gedurende 3 jaar follow-up.

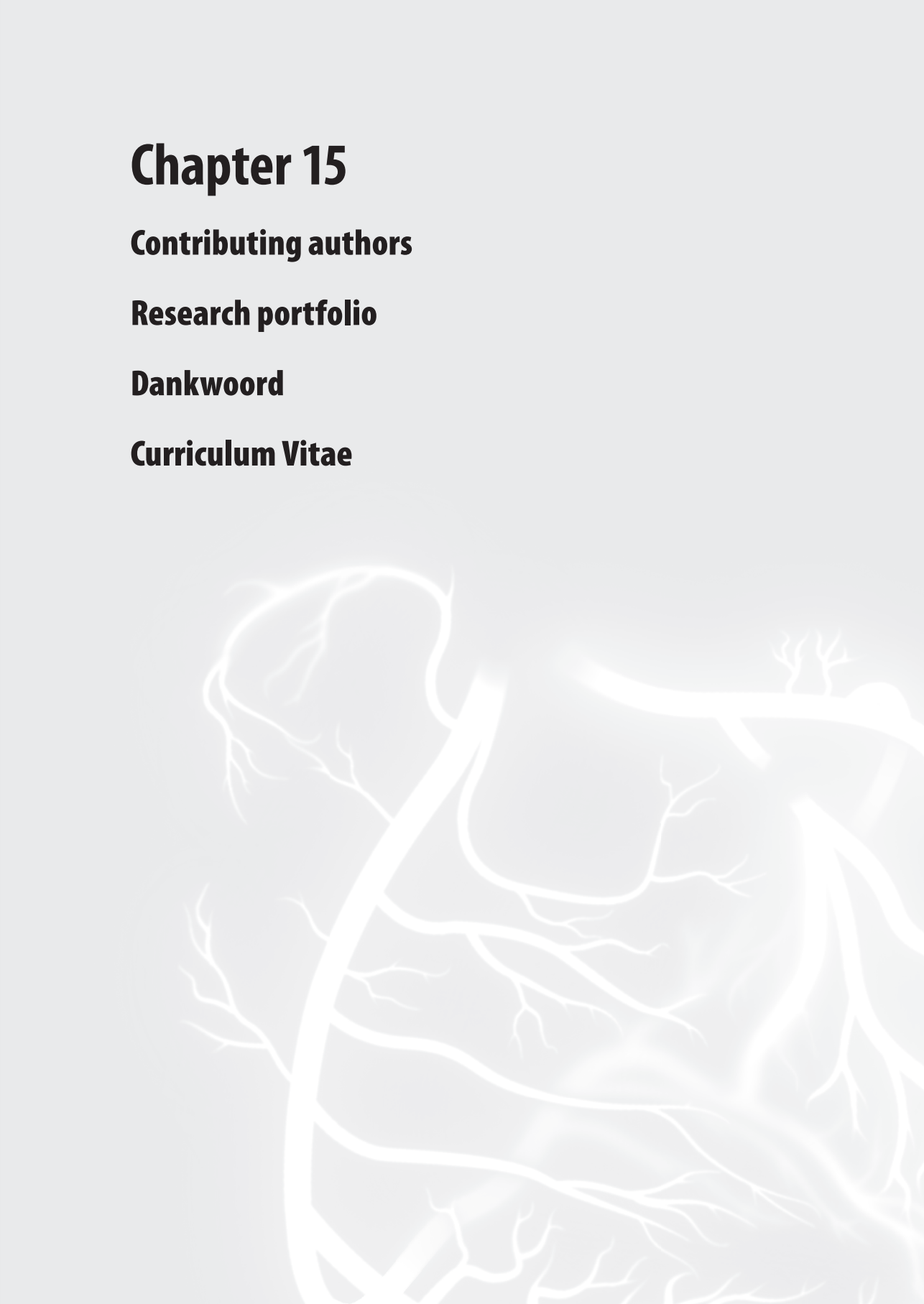
Chapter 15

Contributing authors

Research portfolio

Dankwoord

Curriculum Vitae



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Courses	year	workload (ECTS)
CVOI course: Interventional Cardiology	2009	0.2
Hands-on course in cardiovascular MRI	2009	0.3
ECG course AMC	2009	0.3
Clinical epidemiology	2009	0.7
Wellens ECG course	2010	0.2
Clinical Data Management	2010	1.0
CVOI cursus: Acute Coronary Syndromes	2010	0.2
Clinical Data Management	2010	0.2
Summer program Erasmus university	2010	2.0
-introduction to Data-analysis		
-regression analysis		
-survival analysis		
Advanced Biostatistics AMC	2011	1.1
Wellens ECG course	2011	0.2
Basic Course Legislation and Organization for Clinical Researchers	2012	0.9
Teaching		
ECG course for nurses	2010-2014	4.0
Conferences		
Monthly meeting journal club	2013	1.9
Monthly research meeting	2009-2016	2.5
ESC conference	2009-2014	10.0
TCT conference	2009-2014	10.0
ACC conference	2009-2014	10.0
NVVC conference	2009-2011	1.5
Oral Presentations		
Predictive value of plasma glucose level on admission for short and long term mortality in STEMI patients treated with primary PCI. Presented at ESC.	2010	2.0

Courses	year	workload (ECTS)
Impact of Multivessel Disease with and without a Coexisting Chronic Total Occlusion on Short and Long-Term Mortality in STEMI Patients with and without Cardiogenic Shock. Presented at ACC.	2011	2.0
The Impact of the Location of a Chronic Total Occlusion in a non-Infarct Related Artery on Long-term Mortality in ST-Elevation Myocardial Infarction Patients. Presented at TCT.	2011	2.0
Poster Presentations		
Long-Term Mortality in Insulin Dependent Versus Non-Insulin Dependent Diabetic ST Elevation Myocardial Infarction Patients after Primary Percutaneous Coronary Intervention. Presented at ACC.	2010	0.5
Age and One-Year Mortality After ST Elevation Myocardial Infarction Treated With Primary Percutaneous Intervention. Presented at Dutch society of cardiology.	2010	0.5
The impact of the Location of a Chronic Total Occlusion in Conjunction with the Location of the Infarct Related Artery on Long-term Mortality in ST-Elevation Myocardial Infarction Patients. Presented at TCT.	2011	0.5
Long-Term Clinical Outcomes after Percutaneous Coronary Intervention for Chronic Total Occlusions in Elderly Patients (≥75 years): Five-Year Outcomes from a 1,791 Patient Multi-National Registry. Presented at TCT.	2012	0.5

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1 JP Henriques, LP Hoebers, T Ramunddal, P Laanmets, E Eriksen, M Bax, D Ioanes, MJ Suttorp, BH Strauss, E Barbato, R Nijveldt, AC van Rossum, KM Marques, J Elias, IM van Dongen, BE Claessen, JG Tijssen, RJ van der Schaaf, and for the Explore trial investigators, The impact of percutaneous intervention for concurrent chronic total occlusion on left ventricular function in ST elevation myocardial infarction (EXPLORE): a randomized multicenter trial. *submitted to J. Am. Coll. Cardiol.* (2016).

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DANKWOORD / ACKNOWLEDGEMENTS

Wetenschappelijk onderzoek is nooit een individuele inspanning. Het vergt toewijding en energie op elk niveau van de gezondheidszorg. Te beginnen de patiënten die bereidwillig moeten zijn om een onderzoek te ondergaan, de artsen en verpleegkundigen die samen met de onderzoeker de studiehandelingen moeten verrichten 24 uur per dag, 7 dagen in de week. De cardiologie maar ook de radiologie afdeling waar ik menig uur heb doorgebracht. Ik ben me hier terdege van bewust en wil daarom iedereen die direct of indirect betrokken is geweest bedanken voor hun hulp bij de totstandkoming van mijn proefschrift. Graag wil ik nog enkele personen in het bijzonder bedanken.

Allereerst mijn copromotor dr. J.P.S. Henriques. Beste José, natuurlijk zet ik jou bovenaan aangezien we het gehele traject zo nauw hebben samengewerkt. Thuis refereerde ik wel eens naar je als ''mijn tweede vader'' aangezien je adviezen en begeleiding veel verder reikt dan mijn wetenschappelijke carrière en waarvoor dit dankwoord veel te klein is. Je bent een bijzonder persoon met ''allround'' kwaliteiten waarvoor ik een groot respect heb. Je beschikt over een zeer grote mensenkennis waarmee ik weinig voor je verborgen kon houden en je mij altijd de juiste richting in hebt gestuurd. Onze samenwerking is altijd gebaseerd op wederzijds vertrouwen waarbij we onze ongezouten eerlijke mening konden geven. Dit heb ik altijd erg gewaardeerd. Ik kijk uit naar alle toekomstige projecten die we nog samen zullen doen.

Mijn promotor prof. dr. J.J. Piek, beste Jan, als een van mijn promotoren heb jij altijd het overzicht gehouden omtrent de vorderingen van mijn promotie. In mijn laatste jaar heb ik nog het genoegen gehad om samen een project van de grond te krijgen. Je hartelijke persoonlijkheid en je enthousiasme waarmee je jouw kennis overbrengt werken erg motiverend en aanstekelijk.

De overige leden van mijn promotiecommissie: prof. mr.dr. B.A.J.M. de Mol, prof. dr. R.J.G. Peters, prof. dr. R.J. de Winter, prof. dr. N. van Royen, prof. dr. M.J. de Boer en prof. dr. P. van der Harst wil ik bedanken voor het kritisch beoordelen van mijn proefschrift en voor hun bereidheid zitting te nemen in mijn promotiecommissie.

Dr. R. van der Schaaf, beste René, eigenlijk heb ik deze promotieplek aan jou te danken. Ik leerde je kennen in het OLVG, waar ik als coassistente probeerde te excelleren om zo mijn droom om cardioloog te worden te bewerkstelligen. Ik was al aardig op weg totdat jij me op een dag je kantoor binnen riep waar jij op je computer de EXPLORE trial aan mij presenteerde, een trial waar jij samen met Jose PI van was. Jee, promoveren…was

dat wel iets voor mij? Maar eigenlijk was ik meteen verkocht en paste het precies bij mij. Dank voor je inzicht op dat moment.

Prof. dr. J.G.P. Tijssen, beste Jan, toen ik net in het AMC kwam werken werd jij door de collega's geïntroduceerd als de ''vader'' van de groep en niets bleek minder waar. Als alwetende professor was en ben jij de vraagbaak van elke promovendus en zo heb jij de afgelopen jaren veel vooraanstaande cardiologen in Nederland mogen ''opvoeden'' en begeleid tot wat ze nu zijn. Ik prijs mezelf gelukkig dat ik nog onder je hoede heb mogen zijn voordat je met pensioen ging. Ook al moesten we vaak voor je deur ''posten'' om je te spreken, je was altijd bereid om advies te geven waar ik in Zweden dankbaar gebruik van heb gemaakt. Hoewel je nu aan het genieten bent van je vrije tijd, kan je de vader-rol gelukkig niet goed loslaten en ben je nog regelmatig op de afdeling Cardiologie te vinden.

Dr. T. Råmunddal & prof. dr. E. Omerovic. Dear Truls, as a highly esteemed member of the EXPLORE investigator team the collaboration grew very strong. As CTO enthusiasts we were eager to find some answers to the critically raised points by our ''opponents''. Furthermore, validating the CTO findings of the single center AMC cohort in SCAAR was our ultimate dream for which you invited me to Gothenborg, Sweden. Thank you for your effort to make this possible. In Sahlgrenska you introduced me to your good friend and collegue Elmir Omerovic. Dear Elmir, with you and Truls, we made our goals possible. The road to our first analyses and papers was challenging, often bumpy and contained many sidetracks which resulted in long working days. Frequently, these days were spend in your office, debating with red cheeks our differences in strategy involving epidemiology, statistics but also religion and ethics while adding some beers to lighten things up and cool our minds. I learned many lessons from you, not just work wise but also about life in general for which I am very grateful.

EXPLORE investigators team.
Dear Jaques Koolen, Maarten-Jan Suttorp, Matthijs Bax, Martijn Meuwissen, Koen Marques, Martin van der Ent, Emanuele Barbato, Vegard Tuseth, Erlend Eriksen, Göran Olivecrona, Truls Råmunddal, Dan Ioanes, Bradley Strauss, Olivier Bertrand and Peep Laanmets. Thank you all for keeping the faith in the trial throughout the slow inclusion rate. We could not have done it without your effort! Coordinating this trial made it easier with such good investigators on board. Thank you all for the good times at the many explore meetings and drinks afterwards.

Graag wil ik alle interventiecardiologen alsmede de interventiecardiologen en fellows die inmiddels elders werkzaam zijn bedanken voor al hun inzet om voldoende patiënten

te includeren. Tevens een groot woord van dank aan alle verpleegkundigen, in het bijzonder Esther Scheunhage en het interventie secretariaat Mary-Allen, Mirjam en Ingrid voor hun tomeloze inzet bij de zoektocht naar geschikte patiënten, data verzameling en dataverwerking.

Tijdens mijn promotietraject had ik het voorrecht om zelf mijn MRI-scans te mogen maken bij mijn EXPLORE studie patiënten. Met de ingewikkelde logistiek en vele handelingen was het soms een uitdaging om alles op tijd rond te krijgen. De MRI scanners waren chronisch overvol voor klinisch gebruik maar altijd werd er wel ruimte gemaakt ten behoeve van research. Zondagen, late avonden of vroege ochtenden, het kon allemaal. Maarten Groenink, Raschel Snoeks, Sandra van den Berg- Faay, Anneke Heutinck, Marieke Heman en alle andere MRI laboranten, bedankt voor jullie inzet.

Ik wil graag alle mede-onderzoekers, Judith, Louise, Sébastien, Christian, Veronique, Madelon, Wouter, Zeliya, Nan, Carla, Paul, Mark, Teun, Alexander, Romy, Susan, Paul, Zeliya, Annelieke en Mark bedanken voor de geweldige tijd in het AMC.

Een speciaal woordje natuurlijk voor de interventie onderzoekers Anja, Wichert, Ze-Yie, Kirsten, Peter, Maik, Pier, Tim, Wouter, Mariëlla, Esther, Lu, Robin en alle ''nieuwkomers''. B2-213 is de afgelopen jaren uitgegroeid tot een begrip!! Wat een leuke tijden hebben we beleefd in die kamer. We woonden er praktisch en soms waren we net een kleuterklas maar werken konden we ook, ook al werd mijn ''stilte uurtje'' niet altijd gewaardeerd. Jongens, echt een toptijd, kan het niet anders verwoorden. Hopelijk zie ik jullie allemaal terug in de kliniek! Enkele interventie collega's wil ik nog even speciaal bedanken. Ties, bedankt dat je mijn cover wilde maken. Het is super mooi geworden! Ronak (a.k.a. ''de Gooische'') de tijd dat je naast me zat was legendarisch. We hadden aan 1 woord genoeg en vaak gaf ik je een lekkere pets op je billen. Super leuk dat je naar Zweden bent gekomen…sindsdien doe je niet meer aan ''wijntje delen''. Annemarie, als mede Henriques team member hebben we veel samen gewerkt en vormden we een goed koppel. Je hebt me altijd bijgestaan als we weer op zondag moesten scannen, terwijl dat door het thuisfront niet altijd in dank werd afgenomen. Echter, ''work hard play hard'' is jouw motto en daar hielden we ons dan ook aan. Dagmar, als opvolger van Annemarie en één van de eerste technisch geneeskundige op onze afdeling moest ik even aan je wennen. Je kijk op de ''interventiecardiologie'' wereld was anders dan gewend. In mijn afwezigheid naar Zweden ben je erg gegroeid en heb je EXPLORE in het AMC heel goed voortgetrokken. Je hebt ook een nieuwe impuls gegeven aan het impella onderzoek. Jouw andere blik is echt een aanvulling. Dank voor al je hulp en inzet, wat soms resulteerde in leuke ''sleep overs'' vanwege onze vroege scantijden en de logistieke achterstand van de NS. Na mij zijn Joelle en Ivo bij team Henriques aangesloten en hebben de workload van

Explore overgenomen, dank hiervoor! Biemmah!! Als jouw opvolger heb ik heel veel van je geleerd en ik ben je heel dankbaar voor al je hulp en energie waarmee je me op weg hebt geholpen met mijn promotietraject! Met ups en downs ontwikkelde jij je tot een goede mentor.

Lieve Yu, dank je voor al je organisatorische adviezen betreffende het regelen van een multicenter trial! Ik kon altijd bij je terecht als ik weer vastliep. Lieveke, als multitasker in het AMC weet jij overall alles vanaf en sta jij ons bij in het regelen van alle administratieve en bureaucratische zin en onzin in het AMC. Daarnaast was het altijd leuk om even te ''buurten" bij jou op de kamer. Dank daarvoor! Anita en Regina, bedankt voor alle ondersteunende hulp en bereidheid om naast jullie eigen taken nog extra werk op je te nemen.

Ik wil graag al mijn vrienden bedanken voor de ontspannende tijden om het harde werken mee af te wisselen. In het bijzonder mijn Geneeskunde vriendinnen: Wanda, Noera, Rianne en Nicole. Bij jullie kan ik altijd terecht voor advies, work or otherwise. Dank hiervoor!

Lieve Frank, jij bent de laatste jaren mijn beste vriend geworden. Jouw zorgzaamheid heeft mij de ruimte gegeven om me te ontwikkelen tot arts en promovendus. Zonder jou had ik het veel zwaarder gehad. Bedankt voor deze mooie tijd, je bent me erg dierbaar.

Beste familie Koning en aanhang. Al voordat ik bij de familie hoorde hadden jullie mij al helemaal in jullie gezin opgenomen. Ik was altijd welkom en ben op menig ski-vakantie mee geweest. Het was dan voor jullie ook geen verrassing dat ik een tijdje later met Arnold over de drempel stapte. Tijdens de skivakantie in 2011-2012 hadden jullie samen met mijn ouders al enkele ''onderonsjes" gehad. Wat jullie al wisten kwamen wij pas enkele maanden later achter. Lieve Ellen, wat ben ik blij dat Joep jou is tegen gekomen. Jij met al je Konings kwaliteiten, vult die van Hoebers perfect aan. Ik ben blij dat ik je dubbel heb!

Lieve Joep, als jouw favoriete (schoon)zusje ben ik echt, echt, echt enorm trots op je! Jij bent mijn wannabe alter-ego. Met je warme en outgoing persoonlijkheid maak je al mijn muzikale dromen waar. Je bent nog altijd mijn grote broer waar ik tegenop kijk. Je volgt je hart meer dan je verstand. Verander nooit en voor niemand, twijfel nooit aan jezelf, jij bent excellent. Bedankt dat je me bij wilt staan bij mijn verdediging.

Lieve pap en mam, bedankt dat jullie mij altijd zo'n liefdevol thuis hebben gegeven en mij hebben gevormd tot de persoon wie ik nu ben. Zonder jullie had ik dit nooit voor

elkaar gekregen. Ook al hadden jullie niet altijd precies door waar ik me mee bezig hield kon ik altijd bij jullie terecht. Met ouderlijke adviezen als '' niet vergeten te genieten hè" en bovenal bij elk afscheid ''werk ze, maar niet te hard" vertrok ik altijd weer naar Amsterdam. Familie is je dierbaarste bezit, dat heb ik van jullie geleerd. Ik hoop dat we nog lang van elkaar mogen blijven genieten en ik beloof dat ik ooit terug kom naar het zuiden.

Lieve Arnold: door jou word ik me bewust van het citaat vooraan in mijn proefschrift. Sinds ik jou ken is dat een beetje ons levensmotto. Samen genieten is wat we het beste kunnen! Met jou aan mijn zijde wordt alles intenser en betekenisvoller, vooral nu we een gezinnetje zijn geworden. Ook al wisten onze families het eerder dan wij….jij bent precies wat ik nodig heb. Kus!!

CURRICULUM VITAE

Loes Hoebers is geboren op 30 juni 1983 in het Limburgse Venray, opgegroeid in een liefdevol gezin van 4 met een oudere broer Joep. In een muzikale omgeving kon ze daar onbezorgd opgroeien waarbij ze in 2002 haar eindexamen VWO aan het Dendron college in Horst behaalde. Datzelfde jaar startte zij de studie geneeskunde aan de Universiteit van Amsterdam alwaar ze strak op schema in 2009 haar artsendiploma in ontvangst kon nemen. Al vroeg in haar studie sprak het specialisme cardiologie haar het meest aan welke bevestigd werd bij de co-schappen in het Onze Lieve Vrouwe Gasthuis (OLVG) en het Academisch Medisch Centrum (AMC). Om zich verder te ontwikkelen besloot Loes om in 2009 eerst een promotietraject aan te gaan bij prof. dr. J.J. Piek en dr. J.P.S. Henriques. Dit was een onvergetelijke tijd waarbij er hard gewerkt moest worden, zowel in het AMC, thuis als in Gothenborg Zweden met daarnaast ook tijd voor de nodige ontspanning op de vele netwerkborrels en wereldwijde congressen met dit proefschrift als blijvend resultaat.

Op 1 april 2014 is Loes gestart met de opleiding tot cardioloog. De eerste twee jaren beslaan de vooropleiding interne geneeskunde in het AMC met als opleider prof. dr. S.E. Geerlings, internist, gevolgd door een vier jarige opleiding cardiologie in het AMC met als opleider dr. M.M. Vis, cardioloog.