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Performance and safety outcomes of a structured chronic total occlusion (CTO) PCI program

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TABLE OF CONTENTS

THESIS OUTLINE

This Master thesis in Medicine consists of an Original Scientific Article, written between March 2019 and February 2020.

This article was written with the goal of submission to the *Revista Portuguesa de Cardiologia*. The instructions for the authors of this journal are presented in Appendix 1 and correspond to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" of the International Committee of Medical Journal Editors (ICMJE).

RESUMO

Introdução

Oclusão total crónica (CTO) é encontrada por rotina em doentes que são submetidos à angiografia coronária. Nos últimos anos as taxas de sucesso das intervenções coronárias percutâneas (PCIs) nestes doentes tem aumentado, resultado das melhorias técnicas e de materiais utilizados, sem comprometer, contudo, a segurança do doente. Tivemos como objetivo descrever as características, os aspetos procedimentais e os resultados clínicos de um programa estruturado de PCI CTO.

Métodos

Conduzimos um estudo prospetivo de coorte, incluindo todos os doentes consecutivos que entraram no nosso programa desde Dezembro de 2013. Foram recolhidos dados angiográficos e clínicos. Definimos o outcome primário para segurança como as complicações peri-procedimentais e o outcome primário para eficácia como o sucesso procedimental. Foi conduzido um follow up mediano de 508 dias. Os endpoints secundários analisados em follow up incluíram morte, enfarte agudo do miocárdio (EAM) e revascularização da lesão alvo; classes CCS e NYHA; fração de ejeção do ventrículo esquerdo (LVEF).

Resultados

195 doentes com um total de 202 CTOs foram incluídos. Maioria era hipertensa (79.3%), tinha dislipidemia (82.4%) e um índice de massa corporal (IMC) >25.kg.m^{-2} (87.1%); 35.6% eram diabéticos, 32.6% eram fumadores e um terço tinha antecedentes pessoais de EAM. A indicação para CTO PCI era angina em 78.0%, insuficiência cardíaca em 9.2% e arritmias ventriculares em 1.2%. Doença coronária multivaso era presente em 54.5%. Em termos da técnica utilizada, 89.7% foram abordados por via anterógrada com escalonamento de fios. O score J-CTO médio foi de 2.0±0.8, mostrando maior capacidade em prever o sucesso procedimental que o score EuroCTO (CASTLE).

A taxa de sucesso das intervenções foi de 92.8% (85.6% na primeira tentativa). O outcome primário para a segurança ocorreu em 9 doentes. Durante o seguimento, 7 doentes morreram (2 de causa cardiovascular). Admissão pelo EAM ocorreu em 3 doentes. Revascularização da lesão alvo ocorreu em 5 doentes. Grau CCS decresceu após CTO PCI com sucesso em 90.3% dos doentes (2.1 ±0.9 vs 0.6±0.6, p<0.01). Houve uma subida significativa do LVEF em follow up (48,73±10% vs. 52,55±8,26%, p=0.01).

Conclusão

Durante a implementação de um programa dedicado a CTO PCI, atingiu-se uma elevada taxa de sucesso e uma baixa taxa de complicações. CTO PCI com sucesso foi associado a um importante alívio sintomático e um aumento significativo do LVEF. Score J-CTO permanece o melhor preditor de sucesso da intervenção em causa, pelo que o uso de outros e mais complexos scores não mostrou ser vantajoso.

Palavras-Chave:

Oclusão total crónica, Intervenção coronária percutânea, Revascularização, Doença arterial coronária, Seguimento.

PERFORMANCE AND SAFETY OUTCOMES OF A STRUCTURED CHRONIC TOTAL OCCLUSION (CTO) PCI PROGRAM

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ABBREVIATIONS

6MWT: 6-minute walk test

BMI: body mass index

CABG: coronary artery bypass grafting

CCS: Canadian cardiovascular society

CMR: cardiac magnetic resonance

CRF: chronic renal failure

CTO: chronic total occlusion

CV: cardiovascular

CVA: cerebral vascular accident

LBBB: left bundle branch block

LVEF: left ventricular ejection fraction

MACCE: major adverse cardiac and cerebrovascular events

MACE: major adverse cardiac events

MI: myocardial infarction

MT: medical therapy

NYHA: New York heart association

PCI: percutaneous coronary intervention

TIMI: thrombolysis in myocardial infarction

TVR: target lesion revascularization

URL: upper reference limit

ABSTRACT

Background

Coronary chronic total occlusions (CTOs) are routinely found in patients undergoing coronary angiography. In recent years, the success rate of CTO intervention has increased, driven by advances in material and interventional techniques, without compromising patient safety. We aimed to describe the characteristics, procedural aspects and clinical outcomes of a structured CTO program.

Methods

We conducted a prospective, cohort study including all consecutive patients enrolled in our CTO program since December 2013. Angiographic and clinical data were collected. We defined a co-primary safety outcome as procedure-related complications and a co-primary efficacy outcome as procedural success. A follow-up with a median duration of 508 days was conducted. Secondary, exploratory endpoints during the follow up included death, myocardial infarction (MI), target lesion revascularization (TVR), CCS grade, NYHA class and impact on left ventricular ejection fraction (LVEF).

Results

A total of 195 patients with 202 CTO lesions were included. Most patients were hypertensive (79.3%), had dyslipidemia (82.4%) and a body mass index (BMI) > 25.kg.m^2 (87.1%); 35.6% were diabetic, 32.6% were smokers and a third had a prior history of MI. The indication for a CTO PCI was angina in 78.0%, viable heart failure in 9.2% and ventricular arrhythmias in 1.2%. Multi vessel coronary disease was present in 54,5%. Regarding the technical procedure, 89.7% of PCI CTOs were performed via the anterograde approach with wire-escalation technique. The mean J-CTO score was 2.0±0.8. J-CTO and not EuroCTO (CASTLE) score predict successful CTO PCI.

The overall success rate for CTO PCIs was 92.8% (85.6% with one attempt). The primary safety co-endpoint occurred in 9 patients (4.0%). During follow up, 7 patients (4.6%) died (2 of cardiovascular causes). Admissions for MI occurred in 3 patients (1.5%). TVR occurred in 5 patients (2.6%). CCS grade decreased following a successful CTO treatment in 90.3% of patients (2.1 ±0.9 vs 0.6±0.6, p<0.01). LVEF significantly increased (48,73±10% vs. 52,55±8,26%, p=0.01) after a successful CTO intervention.

Conclusions

During implementation of a dedicated CTO PCI program a high success rate with low rate of complications were achieved. A successful CTO PCI was associated with important symptomatic relief and a significant increase in LVEF. J-CTO score remains the best predictors of successful CTO and the use of other more complex scores did not seem to be advantageous.

Keywords

Chronic total occlusion, Percutaneous coronary intervention, Revascularization, Coronary artery disease, Follow up.

INTRODUCTION

Chronic total occlusions (CTOs) are present in approximately 15–25% of patients undergoing coronary angiography and in 25–50% of those with significant coronary disease [1]. Historically, these lesions have often been managed either with medical therapy (MT) or coronary artery bypass grafting (CABG) because of their complexity and low interventional success rates. Previous studies showed that only a minority of CTO patients underwent percutaneous coronary intervention (PCI) (10-11%), being most of them treated with a conservative MT (49-67%) or referred to CABG (25 -40%) [2,3].

Over the past decade, introduction of a variety of dedicated CTO devices combined with advances in interventional techniques and operator experience have led to higher rates of procedural success, without sacrificing patient safety. With contemporary equipment and techniques, high success rates (85% to 90%) are achieved at experienced centers [4]. However, success rates in unselected populations remain low: 61.3% in the New York State PCI Registry and 59% in the U.S. National Cardiovascular Data Registry (vs. 96% in non-occlusive lesions) [5,6]. Therefore, there is a gap between what is achieved at dedicated CTO centers and the outcomes at less experienced centers. Bridging this gap remains a challenge and should be a major focus of current research.

Several observational studies showed a clinical benefit of CTO PCI by improving angina, dyspnea, depression and exercise capacity. These studies also suggested lower mortality, lower incidence of major adverse cardiac events (MACE) and lower risk for arrhythmias [1].

Achieving clinical benefit in CTO PCI requires the procedure to be successful. Accurate scoring systems to grade the difficulty of cases is a valuable tool for appropriate case selection and planning. The first CTO PCI score was the J-CTO (Multicenter CTO Registry of Japan) score that was developed to estimate the likelihood of successful guidewire crossing within the first 30 min of the procedure, based on 5 criteria [7]. Other scores proposed include the PROGRESS-CTO, RECHARGE, CL score and ORA scores [8-11]. One study showed that the various scores had similar predictive capacity for technical success and that they performed better in antegrade-only cases [12]. More recently, Szijgyarto et al [13], using the EuroCTO registry, analyzed the factors influencing technical success and derived and validated a simple model to predict a successful CTO PCI, EuroCTO (CASTLE) score.

Our purpose was to evaluate the peri-procedural revascularization results and clinical outcomes of a structured CTO program and evaluate the predictive power of two CTO stratification scores, J-CTO and EuroCTO.

METHODS

Study population

We conducted a prospective, observational cohort study including all consecutive patients enrolled in a CTO program implemented since December 2013 in tertiary care hospital. The choice of the appropriate CTO revascularization technique took into account the angiographic characteristics of the lesions and operator skills with an antegrade or a retrograde technique. The sequence of use of these wiring techniques and the guidewire selection was completely left to the operator's discretion.

After collecting an informed consent, the participating physicians prospectively inserted all data into a database. Clinical data included patients age, risk factors, previous history of myocardial infarction, chronic renal failure (CRF) (defined as an estimated creatinine clearance <60 mL/min), clinical presentation, left ventricular ejection fraction (LVEF) and ischemia/viability results. Angiographic data included the CTO artery, presence of multi-vessel coronary disease, the SYNTAX score and the Japanese CTO (J-CTO) score. Procedural data were also collected: location of vascular access, the used technique, result of PCI and peri-procedural complications.

Coronary CTOs were defined as complete occlusion (thrombolysis in myocardial infarction (TIMI) grade 0 flow) of at least 3 months duration, in a major coronary artery [2]. J-CTO score calculation was performed according to the original description by Morino et al [7]. Morphology of the entry point was classified as "tapered" if the occluded segment ended in a funnel-shaped form or "blunt" if it did not; occlusion length was measured from the proximal occlusion to the distal retrograde filling from contralateral collaterals and was estimated from angiographic projections visually with single or dual-contrast injections; presence of calcification was visually estimated on fluoroscopy. The degree of development of retrograde collaterals was based on a collateral grading system of 0 to 3, according to the Rentrop and Cohen classification [14].

Follow up and endpoints

The follow-up was performed either by a clinical visit or hospital database consultation and had a median duration of 508 days (interquartile range 278-1084 days).

Data regarding major adverse cardiac and cerebrovascular events (MACCE) occurrence, Canadian cardiovascular society (CCS) angina grade, NYHA class assessment and impact on LVEF were collected. The study was carried out in accordance to the Helsinki declaration; the ethics committee approved the protocol.

We defined a co-primary safety outcome as a procedure-related complications – vessel dissection, side branch occlusion, thrombosis, perforation, ventricular arrhythmia, myocardial infarction (MI), cerebral vascular accident (CVA), vascular access complications and death. A co-primary efficacy outcome was set as a procedural success, defined as a final residual stenosis <30%, with an anterograde TIMI flow grade 3 after stent implantation [2].

Secondary, exploratory endpoints included death, MI, target lesion revascularization (TVR); CCS grade and NYHA class assessment; impact on LVEF on follow up. Criteria for acute MI followed the new universal definition of MI: detection of a rise of cardiac biomarker values (cardiac troponin with at least one value above the 99th percentile upper reference limit (URL)) combined with either symptoms of ischemia, new or presumed new significant ST-segment or T-wave changes, new left bundle branch block (LBBB), development of pathological Q-waves in the electrocardiogram, new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.

Statistical analysis

Categorical variables are presented as a percentage and continuous variables with normal distribution as mean ± SD, otherwise as median with interquartile range was used. Categorical variables were compared using the Fisher's exact test. A *p*-value 0.05 was considered statistically significant. A hierarchical multivariable logistic regression model was used to evaluate independent correlates of successful CTO PCI among patients undergoing CTO PCIs.

RESULTS

Baseline characteristics of population and procedural aspects

A total of 195 patients (mean age 66±10 years, 81% male) with 202 CTO lesions were included. Baseline characteristics and clinical information of study population are shown in Table 1. Most patients were hypertensive (79.3%), had dyslipidemia (82.4%) and a body mass index (BMI) > 25 kg/m^2 (87.1%); 35.6% had diabetes mellitus type 2, 32.6% were smokers and a third had a prior history of MI. The indication for a CTO procedure was refractory angina in 78.0%, heart failure with viable myocardium in 9.2% and refractory ventricular arrhythmias in 1.2%.

Table 1 Baseline characteristics and clinical information of study population

Characteristic	
Patients, n	195
Age, years (mean ± SD)	66±10
Male sex (%)	81.0
Smoking (%)	32.6
Diabetes mellitus type 2 (%)	35.6
Dislipidemia (%)	82.4
Arterial hypertension (%)	79.3
BMI > 25 kg/m^2 (%)	87.1
Previous MI (%)	30.0
Indication for CTO PCI	
Angina (%)	78.2
Viable heart failure (%)	9.2
Ventricular arrhythmias (%)	1.2

BMI denotes body mass index; MI, myocardial infarction.

Table 2 shows the procedural details of the CTO procedures. The occluded artery was more frequently the right coronary artery (42%) in comparison with left anterior descending (37%), followed by the left circumflex (20%). In 89.5% of cases, CTO PCI was attempted for the first time, while 10.6% of cases had more than one previous failed attempt; 54.5% of patients had multivessel disease. Contralateral injection was used in half of the cases (51.3%). Regarding the technical procedure, 89.7% of PCI CTOs were performed via the anterograde wire-escalation technique; dissection re-entry technique was used in a minority of antegrade cases (2.4%). A retrograde strategy was utilized in 10.3% of cases in our cohort. Intravascular imaging with intravascular ultrasound was performed in 17.2% of cases. The mean J-CTO score was 2.0±0.8.

Table 2 Procedural details of CTO PCI

Characteristic	
Procedures, n	202
Target artery:	
Right coronary (%)	42.1
Left anterior descending (%)	37.9
Left circumflex (%)	20.0
Multivessel disease (%)	54.5
Bilateral injection (%)	51.3
Anterograde wire escalation technique (%)	89.7
Retrograde technique (%)	10.3
Intravascular imaging use (%)	15.3
IVUS (%)	17.2
J-CTO score (mean ± SD)	2.0±0.8

IVUS denotes intravascular ultrasound.

Primary and secondary endpoints

The primary efficacy co-endpoint (procedure success rate) occurred in 92.8% of patients (in 85.6% at the first attempt). The primary safety co-endpoint occurred in 4.0% of patients (9 patients) and included: stroke in peri procedural period in 1 patient, perforation in 3 patients (1 needed pericardiocentesis), local hematoma in 2 patients and distal embolization/important side branch occlusion in 3 patients.

Secondary endpoints incidence during follow-up included 7 (4.6%) mortality events, 2 of them cardiovascular deaths (not-procedure related). Admissions for MI occurred in 3 patients (1.5%). TVR occurred in 5 patients (2.6%) (Table 3).

Table 3 Primary and secondary endpoints

Procedure related endpoint	
Procedure success (%)	92.8
Procedure Complications, n (%)	9 (4.0)
Stroke, n	1
Perforation, n	3
Local hematoma, n	2
Side branch occlusion, n	3
Follow up	
Global mortality, n (%) / CV death, n (%)	6 (4,0) / 2 (2,2)
MI, n (%)	3 (1,5)
TVR, n (%)	5 (2,6)

CV denotes cardiovascular; MI, myocardial infarction; TVR, target vessel revascularization.

Regarding symptoms, the CCS grade decreased following a successful CTO treatment in 90.3% of patients (2.1 ±0.9 vs 0.6±0.6, p<0.01) (Figure 1). Regarding LVEF, we found a significant increase (48,73±10% vs. 52,55±8,26%, p=0.01) after a successful CTO intervention (Table 4).

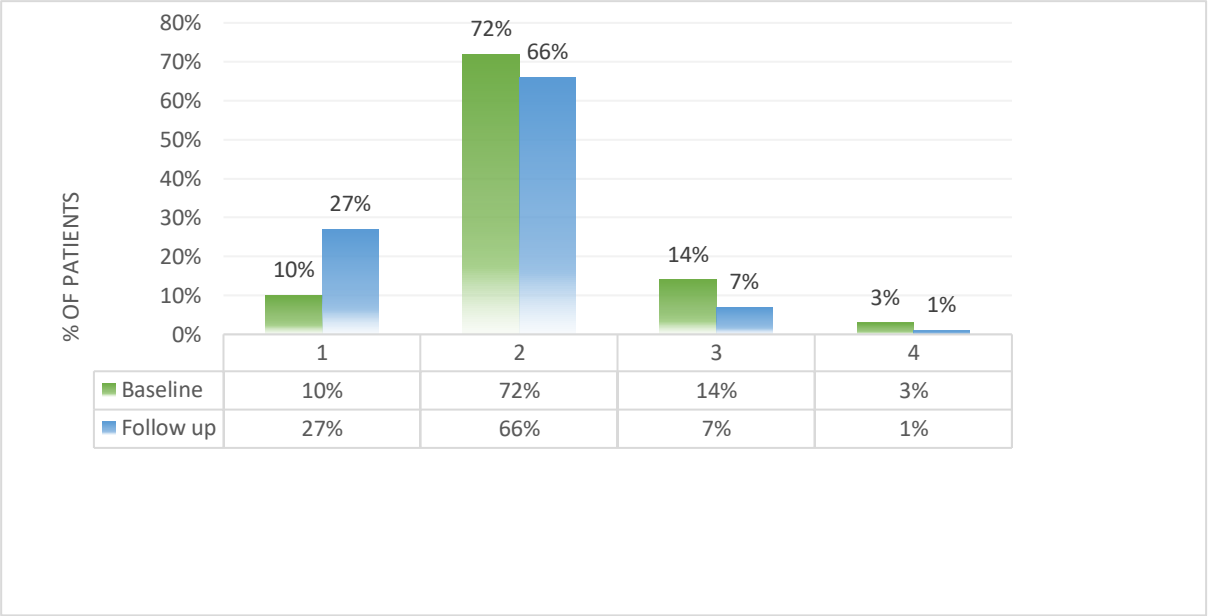

Figure 1 CCS grade before CTO PCI and on follow up

Table 4 NYHA class and LVEF before CTO PCI and on follow up

Variable	**Baseline**	**Follow up**	***P*-value**
NYHA class			
I	42.9%	81.6%	0.08
II	46.4%	12.3%	
III	10.7%	4.1%	
IV	0%	0%	
LVEF (mean ± SD)	48,73±10%	52,55±8,26%	**0.01**

LVEF denotes left ventricular ejection fraction

Comparison of demographics and risk factors of patients with successful and failed CTO PCIs

In Table 5, we compare the characteristics of patients with failed CTO PCI and patients with a successful CTO PCI. Both groups were similar regarding cardiovascular (CV) risk factors prevalence and baseline clinical characteristics. The presence of a higher J-CTO score and the use of bilateral injection were predictors of success in univariate analysis.

Table 5 Comparison of demographics and risk factors for patients with successful and failed CTO PCIs

Variable	Successful CTO	Failed CTO	*P*-value
Age, per year (mean)	65.5	66.7	0,51
Male sex (%)	80.4	87.1	0.37
BMI >25 kg/m^2	28.2	28.5	0.73
Arterial hypertension (%)	79.3	77.4	0.80
Diabetes mellitus type 2 (%)	36.4	51.6	0.10
Dyslipidemia (%)	82.1	90.3	0.26
Chronic kidney disease (%)	17.5	15.8	0.86
Previous MI (%)	50.9	53.6	0.79
SYNTAX score	19.3	18.3	0.73
LVEF (%)	48.5	49.9	0.44
J- CTO score, per unit	1.8	2.4	**0.01**
EuroCTO (CASTLE) score, per unit	1,6	1,7	0.88
Retrograde approach (%)	73.1	22.6	0.05
Bilateral injection (%)	51.1	32.3	**0.03**

BMI denotes body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

On a hierarchical multivariable logistic regression model (Table 6), we found that the only significant independent predictor of success was the J-CTO score. We also evaluated the performance of a new EuroCTO (CASTLE) score, but it did not show better discriminative capacity than the commonly utilized J-CTO.

Table 6 Significant risk factors for CTO PCI success: hierarchical multivariable logistic regression model

Variable	Hazard ratio (95% CI)	*P*-value
Age, per year	0.969 (0.907-1.035)	0.348
Male sex	0.611 (0.118-3.178)	0.558
Arterial hypertension	1.061 (0.244-4.613)	0.937
Diabetes mellitus type 2	1.117 (0.358-3.482)	0.849
Chronic kidney disease (%)	1.095 (0.230-5.231)	0.909
J-CTO score, per unit	0.145 (1.662-28.806)	**0.008**
EuroCTO (CASTLE) score, per unit	2.007 (0.845-4.763)	0.114
Bilateral injection	3.046 (0.974-9.525)	0.056

CI denotes confidence interval.

DISCUSSION

In this study, we present the results of the implementation of a dedicated CTO PCI program in a tertiary care center. The prevalence of male gender and traditional CV risk factors is high and as reported in other studies. Notably, more than fifty percent of our population had a multi vessel coronary disease and multiple CTO lesions affected 9.1% of patients. These findings were like those reported in the European Registry of CTOs (ERCTO registry), confirming that CTO lesions are associated with an extensive atherosclerosis burden. Differently from Canadian multicenter CTO and Italian registries [2,3,15], where only 13% reported no or only mild symptoms (CCS class 0/1) and where almost a quarter of patients were completely asymptomatic, respectively, in our cohort >90% of patients had angina or symptoms of heart failure.

The overall success rate for CTO PCIs was 92.8% (86% with one attempt). With contemporary equipment and techniques, high success rates (85% to 90%) are achieved at experienced centers. However, there is a gap between what is achieved at dedicated CTO PCI centers and the outcomes at less experienced centers. An annual volume of at least 500 PCIs with a presence of a CTO operator was a prerequisite for each study center in Decision CTO trial [16]. This inclusion criteria highlight the importance of a structured program implementation for success of procedure.

In our cohort, the CCS grade and NYHA class decreased following a successful CTO treatment. In the OPEN-CTO registry, that analyzed 1.000 consecutive patients undergoing CTO PCI with the hybrid approach using standardized questionnaires, a 10.8 points (95% CI: 6.3 to 15.3) improvement in the quality-of-life domain of the Seattle Angina Questionnaire was observed among successful versus unsuccessful procedures ($p < 0.001$) [17]. Peri-Okonny et al [18], including 869 patients enrolled in this registry, showed that the proportion of patients that exercised regularly increased from 33.5% at baseline to 56.6% 12 months after CTO PCI ($p<0.01$). Rossello et al [19], in a prospective study including 47 consecutive patients with successful percutaneous recanalization of CTO underwent adenosine stress cardiac magnetic resonance (CMR), 6-minute walk test (6MWT), and the Short Form-36 Health Survey before and 6 months after the procedure. A successful recanalization of a CTO was followed by a significant improvement of global physical and mental health status, the distance walked in the 6MWT, the incidence of chest pain at the end of the 6MWT and the ischemic burden index evaluated by CMR. Additionally, patients with greater CMR ischemic index before PCI showed better improvement in the 6MWT. Two other studies [20,21] performing cardiopulmonary testing before and after CTO PCI showed an increase in peak oxygen consumption and anaerobic threshold after a successful CTO PCI.

Achieving clinical benefit with CTO PCI requires the procedure to be successful. A few scoring systems have been developed over the years to predict successful PCI. Morino et al [7] published the J-CTO score in 2011, derived from 400 CTO cases. This study identified 5 characteristics associated with failure to pass an antegrade guidewire across the occlusion within 30 min. The characteristics included a previous failed attempt and did not include previous CABG (widely recognized to be an adverse feature). More recently, a new tool, the EuroCTO (CASTLE) score [13] was derived and validated from the Euro CTO registry and seems to have a greater discriminative capacity, compared with the widely used J-CTO score. It incorporates 4 factors that are included in J-CTO - stump anatomy, tortuosity, length of occlusion and extent of calcification. Importantly, however, it also includes 2 additional variables - prior CABG and age, both of which are objective and not open to operator interpretation. In our cohort, however the application of this score did not present greater discriminative capacity regrading J-CTO score. Furthermore, none of clinical characteristic was predictor of a successful PCI. The only factors that independently predict the success of CTO PCI were the characteristics of lesion as assessed by J-CTO score and the use of bilateral injection.

LIMITATIONS

Limitations of our study include the fact that it is limited to a single center, so the findings may not be generalizable. Angiographic data were obtained by visual assessment rather than by quantitative coronary analysis, thus, we cannot eliminate operator-related bias. We did not use stress testing to determine the impact of CTO treatment in functional class or CCS grade. As a result, we cannot exclude a placebo effect.

CONCLUSIONS

During the implementation of a dedicated CTO PCI program, a high success rate with a low rate of complications were achieved. A successful CTO recanalization was associated with a significant symptomatic relief and a significant increase in LVEF. The J-CTO score remains the best predictor of a successful CTO.

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APPENDICES

APPENDIX 1

IV. Manuscript Preparation and Submission

A. Preparing a Manuscript for Submission to a Medical Journal

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs: examples include CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), and STARD for studies of diagnostic accuracy (http://www.equator-network.org/reporting-guidelines/stard/). Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data: this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network (www.equator-network.org/home/) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information. Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word

cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance. Authors should use neutral, precise, and respectful language to describe study participants and avoid the use of terminology that might stigmatize participants.

ii. Technical Information

Specify the study's main and secondary objectives—usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (e.g., percentages) but also as the absolute numbers from which the derivatives were calculated. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Authors should avoid citing articles from predatory or pseudo-journals. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published

papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Published articles should reference the unique, persistent identifiers of the datasets employed.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications (https://www.ncbi.nlm.nih.gov/pubmed/?term=retracted+publication+[pt]).

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.nchi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

k. Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For radiological and other clinical and diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Before-and-after images should be taken with the

same intensity, direction, and color of light. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

B. Sending the Manuscript to the Journal

Manuscripts should be accompanied by a cover letter or a completed journal submission form, which should include the following information:

A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor address the situation. See also Section III.D.2.

A statement of financial or other relationships and activities that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form. See also Section II.B.

A statement on authorship. Journals that do not use contribution declarations for all authors may require that the submission letter includes a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work if that information is not provided in another form See also Section II.A.

Contact information for the author responsible for communicating with other authors about revisions and final approval of the proofs, if that information is not included in the manuscript itself.

The letter or form should inform editors if concerns have been raised (e.g., via institutional and/or regulatory bodies) regarding the conduct of the research or if corrective action has been recommended. The letter or form should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications. Doing so may expedite the review process and encourages transparency and sharing of expertise.

Many journals provide a presubmission checklist to help the author ensure that all the components of the submission have been included. Some journals also require that authors complete checklists for reports of certain study types (e.g., the CONSORT checklist for reports of randomized controlled trials). Authors should look to see if the journal uses such checklists, and send them with the manuscript if they are requested.

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