

# Improved Propensity-Score Matched Long-Term Clinical Outcomes in Patients with Successful Percutaneous Coronary Interventions of Coronary Chronic Total Occlusion

Sinisa Stojkovic,<sup>1,2</sup> MD, Stefan Juricic,<sup>1</sup> MD, Milan Dobric,<sup>1,2</sup> MD, Milan A. Nedeljkovic,<sup>1,2</sup> MD, Vladan Vukcevic,<sup>1,2</sup> MD, Dejan Orlic,<sup>1,2</sup> MD, Goran Stankovic,<sup>1,2</sup> MD, Miloje Tomasevic,<sup>1,3</sup> MD, Srdjan Aleksandric,<sup>1</sup> MD, Miodrag Dikic,<sup>1</sup> MD, Milorad Tesic,<sup>1</sup> MD, Zlatko Mehmedbegovic,<sup>1</sup> MD, Nikola Boskovic,<sup>2</sup> MD, Milorad Zivkovic,<sup>1</sup>, Vladimir Dedovic,<sup>1</sup>, Dejan Milasinovic,<sup>1</sup>, Miodrag Ostojic,<sup>2</sup> and Branko Beleslin,<sup>1,2</sup> MD

## Summary

The objective of the study was to evaluate major adverse cardiovascular events (MACE) after successful versus failed percutaneous coronary intervention for chronic total occlusion (PCI-CTO).

Limited data are available on long-term clinical follow-up in the treatment of chronic total occlusion (CTO).

Between January 2009 and December 2010 PCI-CTO was attempted in 283 consecutive patients with 289 CTO lesions. Procedural success was 62.3% and clinical follow-up covered 83% (235/283) of the study population with a median follow-up of 66 months (range, 59-74).

The total incidence of MACE was 57/235 (24.3%), and was significantly higher in the procedural failure group than in the procedural success group (33/87 (37.9%) versus 24/148 (16.2%),  $P < 0.001$ ). All-cause mortality was significantly lower in patients with successful PCI-CTO compared to failed PCI-CTO (10.8% versus 20.7%,  $P < 0.05$ ). Also, the rate of cardiovascular death in the procedural failure group (14.9%) was slightly higher than that in the procedural success group (7.4%,  $P = 0.066$ ). The rate of TVR was statistically higher in the procedural failure group ( $P < 0.009$ ). Propensity score-adjusted Cox regression showed that procedural success remained a significant predictor of MACE (adjusted HR 0.402; 95% CI 0.196-0.824;  $P = 0.013$ ).

Our study emphasizes the importance of CTO recanalization in improving long-term outcome including all-cause mortality with a borderline effect on cardiovascular mortality.

(Int Heart J 2018; 59: 719-726)

**Key words:** Coronary artery disease, Long-term survival, Revascularization

**P**ercutaneous coronary intervention (PCI) of a chronic total occlusion (CTO) is one of the major challenges in interventional cardiology. CTO, defined as a complete arterial occlusion TIMI [Thrombolysis in myocardial infarction] 0 flow] of at least 3 months duration, occurs in approximately 15-30% of all diagnostic coronary angiography procedures,<sup>1,2)</sup> and in 5% of coronary computed tomography angiography studies.<sup>3)</sup> Although the treatment of CTO remains a technical challenge and 20-35% of CTOs are still not revascularized by PCI even when performed by experienced operators,<sup>4,5)</sup> successful PCI of CTO has been shown to improve left ventricular (LV) systolic function, reduce angina, increase exercise capacity, and reduce the need for late by-pass surgery.<sup>4,6,7)</sup> On the other hand, CTO patients who were not revascularized had a significantly higher rate of car-

diac mortality and sudden cardiac death compared with those who were revascularized.<sup>8,9)</sup>

The aim of this single center retrospective study was to compare the long-term outcomes of patients with successful versus unsuccessful PCI of a CTO and to assess the mortality rate related to the location of the occluded vessel.

## Methods

Out of 3040 elective PCI performed from January 1, 2009 until December 31, 2010, we retrospectively analyzed 283 consecutive patients (mean age,  $58.5 \pm 9.5$  years, 81% male) in whom PCI of CTO was attempted. All procedures were performed at the Catheterization Laboratory of the Cardiology Department, Clinical Center

From the <sup>1</sup>Clinic for Cardiology, Clinical Center of Serbia, Belgrade, Serbia, <sup>2</sup>School of Medicine, University of Belgrade, Belgrade, Serbia and <sup>3</sup>School of Medicine, University of Kragujevac, Kragujevac, Serbia.

This study was a part of the Project III 41022 of the Ministry of Education, Science, and Technological Development of Republic of Serbia.

Address for correspondence: Sinisa Stojkovic, MD, Clinic for Cardiology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, 8 Koste Todorovica, Belgrade 11000, Serbia. E-mail: sstojkovi@mts.rs

Received for publication June 27, 2017. Revised and accepted October 2, 2017.

Released in advance online on J-STAGE June 6, 2018.

doi: 10.1536/ihj.17-360

All rights reserved by the International Heart Journal Association.

of Serbia, Belgrade. Follow-up for adverse clinical events was conducted by telephone contact; in the case of an adverse event, an outpatient medical visit was performed and hospital records were collected.

Demographic and clinical characteristics of the study population, angiographic characteristics of the lesions, procedural characteristics of PCI, and procedural complications were collected from our CTO database.

A CTO lesion was defined as an obstruction of a coronary artery with TIMI flow grade 0 with an estimated duration of at least 3 months. Duration of occlusion was estimated on the basis of history of angina, the interval from the last episode of acute coronary syndrome consistent with the location of the occlusion, or proven by previous angiography. Procedural success was defined as final residual stenosis less than 30%, with TIMI grade flow 3.

Major adverse cardiac events (MACE) were defined as cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR), either percutaneous or surgical. All deaths were considered cardiac unless otherwise documented. Non Q-wave myocardial infarction was defined as a creatine kinase-MB enzyme elevation > 3 times the upper limit of the normal value; when new pathological Q waves in addition to enzyme elevation were observed in an electrocardiogram, the event was defined as a Q-wave myocardial infarction. TVR was defined as a repeat revascularization within the treated vessel.

**Statistical analysis:** Categorical variables are expressed as numbers and percentages, and continuous variables as the mean  $\pm$  standard deviation. After testing for normal distribution, differences were compared using the unpaired Student *t*-test, chi-square test, Mann-Whitney test, and/or?? ANOVA where appropriate. Univariable and multivariable logistic regression analyses were used to identify predictors of procedural success.

A propensity score was constructed using binary logistic regression where the dependent variable was procedural success and predictors were clinical and angiographic variables that are known to be related to clinical outcomes (MACE): age, gender, diabetes mellitus, arterial hypertension, smoking, previous MI, previous PCI, coronary artery, CTO length, presence of calcifications, tortuosity, and stump morphology.

A propensity score-adjusted Cox regression was performed to assess the relation between procedural success and MACE, controlling for group differences.

Event-free survival curves for adverse cardiac events were estimated by Kaplan-Meier method and compared by the log-rank test. A *P* value less than 0.05 was considered as statistically significant. All statistical analyses were performed with SPSS version 21.

## Results

**Study population:** The study population consisted of 283 patients with 289 chronic total coronary occlusions in whom percutaneous recanalization was attempted.

The characteristics of the patients are summarized in Table I. Based on procedural success, the patients were divided into two groups: a procedural successful group (*n*

= 178; 63%) and a procedural failure group (*n* = 105, 37%). There were no statistically significant differences in demographic and clinical characteristics between the two groups, except for the higher incidence of a previous myocardial infarction (*P* = 0.023) and lower incidence of unstable angina (*P* < 0.001) in the failure group of patients.

**Angiographic characteristics:** Regarding angiographic characteristics, there were certain differences between the successful and failure groups - lesions longer than 20 mm, more tortuous vessels, and calcifications were all more frequent in the failure group. Furthermore, a side branch at the site of the occlusion, blunt stump morphology, and lower contrast consumption were significantly more frequent in the procedural failure group (Table II). The periprocedural complication rate was similar in both groups (Table III).

Procedural success was achieved in 180 lesions (62.3%), while procedural success was absent in 109 attempts (37.7%). Based on these procedural outcomes, the lesions were divided into two groups: a procedural success group (*n* = 180) and a procedural failure group (*n* = 109). There were no statistically significant differences in procedural characteristics between the 2 groups.

By univariable analysis (Table IV), the following factors were identified as predictors of procedural failure: previous myocardial infarction (*P* = 0.023), occlusion length > 10 mm (*P* = 0.037), occlusion length > 20 mm (*P* = 0.003), presence of tortuosity (*P* < 0.001), mild calcified lesions (*P* = 0.012), moderately calcified lesions (*P* = 0.025), severe calcified lesions (*P* = 0.001), presence of a side branch at the site of occlusion (*P* = 0.004), and blunt morphology of the occlusion (*P* < 0.001). Unstable angina pectoris (*P* = 0.001) and tapered stump morphology (*P* = 0.001) were identified as predictors of procedural success.

Multivariable analysis identified tortuosity (*P* = 0.007), calcifications (*P* < 0.001), and blunt stump as independent predictors of procedural failure, whereas unstable angina pectoris was found to be a predictor of procedural success (*P* = 0.009).

**Overall rate of major adverse cardiovascular events (MACE):** The median follow-up period was 66 months (IQR 59-74). Out of 283 patients, 48 (17%) were lost to follow-up.

The total number of MACE was 57/235 (24.3%), and there were significantly more in the procedural failure group than in the procedural success group (33/87, 37.9% versus 24/148, 16.2%, *P* < 0.001). The all-cause mortality rate was significantly higher in the procedural failure group (20.7%) than in the procedural success group (10.8%, *P* < 0.05). Also, there was a slightly higher rate of cardiovascular death in the procedural failure group (14.9%) than in the procedural success group (7.4%), *P* = 0.066. The rate of TVR (both PCI and CABG) was statistically higher in the procedural failure group (*P* = 0.009) (Table V).

**Non-adjusted analysis:** Procedural success was found to be a significant predictor of MACE by univariable Cox regression analysis (HR 0.423; 95% CI 0.243-0.739; *P* = 0.002).

**Table I.** Demographics and Clinical Characteristics

Characteristic (n (%))	Total number of patients (n = 283)	Procedure Successful (n = 178)	Procedural Failure (n = 105)	P value	OR (95% CI)
Age (years, mean ± SD)	58.5 ± 9.5	58.3 ± 9.6	58.8 ± 9.3	0.69	-
Male	228 (81%)	141 (79%)	87 (83%)	0.45	0.788 (0.423-1.471)
Family history of CAD	129 (46%)	84 (47%)	45 (49%)	0.47	1.191 (0.733-1.937)
Diabetes	69 (24%)	48 (27%)	21 (20%)	0.19	1.447 (0.826-2.642)
Insulin dependent	14 (5%)	8 (4%)	6 (6%)	0.65	0.776 (0.262-2.303)
Hypertension	227 (80%)	144 (81%)	83 (79%)	0.70	1.123 (0.616-2.046)
Hypercholesterolemia	221 (78%)	144 (81%)	77 (73%)	0.14	1.540 (0.870-2.728)
Smoking status					
Never	116 (41%)	73 (41%)	43 (41%)	0.99	1.002 (0.614-1.637)
Smoker	83 (29%)	56 (32%)	27 (26%)	0.30	1.326 (0.773-2.276)
Ex-smoker	84 (30%)	49 (28%)	35 (33%)	0.30	0.760 (0.451-1.281)
Previous MI	181 (64%)	105 (59%)	76 (72%)	0.02*	0.549 (0.326-0.925)
LVEF (%)	45 ± 13	46 ± 14	44 ± 12	0.188	-
LVEF < 40%	94 (33%)	55 (31%)	39 (37%)	0.281	0.757 (0.455-1.257)
Previous CABG	31 (11%)	21 (12%)	10 (10%)	0.55	1.271 (0.574-2.814)
Previous PCI					
Number	189 (67%)	118 (66%)	71 (67%)	0.82	0.942 (0.564-1.574)
Same artery	32 (11%)	21 (12%)	11 (10%)	0.73	1.143 (0.528-2.476)
Other artery	62 (22%)	39 (22%)	23 (22%)	0.99	1 (0.558-1.792)
Stable angina pectoris	168 (59%)	104 (58%)	64 (61%)	0.68	0.9 (0.550-1.473)
Unstable angina pectoris	58 (20%)	48 (27%)	10 (10%)	< 0.01*	3.508 (1.689-7.285)
Number of diseased vessels					
1	131 (46%)	81 (46%)	50 (48%)	0.73	0.919 (0.566-1.490)
2	98 (35%)	63 (35%)	35 (33%)	0.72	1.096 (0.659-1.823)
3	54 (19%)	34 (19%)	20 (19%)	0.99	1.003 (0.543-1.854)
Concomitant therapy					
Beta-blocker	176 (65%)	110 (62%)	66 (63%)	0.859	1.046 (0.636-1.722)
ACE inhibitor and/or					
ARB	230 (81%)	142 (80%)	88 (84%)	0.401	1.312 (0.695-2.477)
Statin	238 (84%)	153 (86%)	85 (81%)	0.266	0.694 (0.364-1.324)
Nitrate	67 (24%)	39 (22%)	28 (27%)	0.363	1.296 (0.741-2.268)
DAPT	283 (100%)	178 (100%)	105 (100%)	-	-
OAT	16 (6%)	9 (5%)	7 (7%)	0.571	1.341 (0.484-3.714)

LVEF indicates left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; and OAT, oral anticoagulant therapy.

**Propensity-score adjusted analysis:** Propensity score-adjusted Cox regression showed that procedural success remained a significant predictor of MACE (adjusted HR 0.402; 95% CI 0.196-0.824;  $P = 0.013$ ).

Kaplan-Meier curves showed significantly better survival without MACE in the group of patients with successful treatment of CTO. Average survival free of MACE time in the procedural success group was  $69 \pm 2$  months and  $56 \pm 3$  months in the procedural failure group (Log rank 15.247,  $P < 0.001$ . HR 2.7, 95% CI 1.610-4.163,  $P < 0.001$ ) (Figure 1).

Although opening a CTO of a target vessel was associated with increased average MACE free time, there was no difference regarding a treated coronary artery (Log rank 2.098,  $P = 0.350$ , LAD compared to Cx HR 2.4, 95% CI (0.690-8.060),  $P = 0.171$ , RCA compared to the Cx HR 0.796, 95% CI (0.313-2.021),  $P = 0.631$ , LAD compared to the RCA HR 1.4, 95% CI (0.787-2.441),  $P = 0.259$ ) (Figure 2).

Figure 3A, B, and C show the Kaplan-Meier survival curves with respect to CTO-PCI success or failure according to the treated vessel. Survival was significantly better

without MACE between CTO-PCI success and CTO-PCI failure in patients with CTO of the left anterior descending artery (LAD). In LAD patients, average survival free of MACE time in the procedural success group was  $72.8 \pm 2.4$  months, and  $59.9 \pm 6.8$  months in the procedural failure group (LogRank 14.638,  $P < 0.001$ ).

There were no differences between CTO-PCI success and CTO-PCI failure in patients with CTO of the right coronary artery (RCA) (Log rank 2.850,  $P = 0.091$ ) or circumflex artery (LCx) (Log rank 1.149,  $P = 0.284$ ).

## Discussion

This was an observational retrospective, nonrandomized study that included 283 patients with 289 CTO lesions, who were treated with PCI during a 2-year period. The main finding of this retrospective analysis is the occurrence of significantly more major adverse cardiovascular events in patients with unsuccessful recanalization of the CTO during long-term follow-up of more than 5 years. The other clinically important finding refers to the independent angiographic characteristics of the patients

**Table II.** Angiographic and Procedural Characteristics

Angiographic characteristic	No of CTO (n = 289)	Procedure successful (n = 180)	Procedure Failure (n = 109)	P value
CTO artery (n (%))				
RCA	137 (47)	81 (45)	56 (51)	0.290
LAD	82 (28)	55 (30)	27 (25)	0.293
Cx	70 (24)	44 (24)	26 (24)	0.909
Localization of CTO (n (%))				
Ostial	25 (9)	19 (10)	6 (6)	0.139
Proximal	94 (32)	56 (31)	38 (35)	0.509
Medial	127 (44)	79 (44)	48 (44)	0.980
Distal	43 (15)	26 (14)	17 (16)	0.790
In-stent CTO (n (%))	16 (5.5)	13 (7)	3 (3)	0.107
Duration of occlusion (months, mean ± SD)	36.6 ± 50.0	34.4 ± 44.6	39.8 ± 56.9	0.507
Diameter of CTO vessel (mm, mean ± SD)	3.0 ± 0.4	3.1 ± 0.4	3.0 ± 0.4	0.673
CTO length (n (%))				
≤ 10 mm	48 (17)	34 (19)	14 (13)	0.181
10-20 mm	73 (25)	53 (29)	20 (18)	0.035
≥ 20 mm	167 (58)	92 (51)	75 (69)	0.003
Tortuosity (n (%))	119 (41)	59 (33)	60 (55)	0.000
Calcification (n (%))				
Mild	180 (62)	102 (57)	78 (72)	0.011
Modest	11 (4)	3 (2)	8 (7)	0.015
Severe	16 (6)	3 (2)	13 (12)	0.000
Stump morphology (n (%))				
Blunt	110 (38)	40 (22)	70 (64)	0.000
Tapered	178 (62)	139 (78)	39 (36)	0.000
Side branch (n (%))	127 (44)	60 (33)	67 (62)	0.003
In-stent CTO (n (%))	16 (5)	13 (7)	3 (3)	0.107
Technical approach				
-Antegrade	271 (93.8)	165 (91.7)	106 (97.2)	0.057
-Retrograde	18 (6.2)	15 (8.3)	3 (2.8)	0.057
Number of wires per lesion	1.5 ± 0.9	1.54 ± 0.8	1.43 ± 0.8	0.447
Fluoroscopic time (minutes)	27.8 ± 22.3	29.3 ± 24.1	24.9 ± 18.2	0.090
Contrast volume (mL)	326 ± 176.9	346.2 ± 170.8	291.4 ± 183.5	0.008

**Table III.** Periprocedural Complications

	n (%)			
Death	0	0	0	-
MI	4 (1.4)	3 (1.7)	1 (0.9)	0.597
Coronary perforation	9 (3.1)	3 (1.7)	6 (5.5)	0.068
Cardiac tamponade	2 (1.4)	1 (0.5)	1 (0.9)	0.719
Vascular complication	7 (2.4)	5 (2.7)	2 (1.8)	0.613
Donor vessel dissection	2 (0.7)	1 (0.5)	1 (0.9)	0.719

MI indicates myocardial infarction.

with failed CTO opening who demonstrated longer occlusions, more tortuous arteries, and calcified lesions with a blunt stump.

Several characteristics of the current study should be highlighted in order to organize a comparison with the results of previous studies and to put the results into a proper perspective. In previous studies, different demographic characteristics were associated with procedural failure. Analysis from the UK Central Cardiac Database<sup>10</sup> reported that age, smoking, increased body mass index, previous CABG, peripheral vascular disease, and previous MI were associated with failure of CTO revascularization. In addition, and similarly to our study, a large Mayo Clinic registry<sup>11</sup> showed a higher incidence of previous

MI and smoking history in the group of patients with procedural failure. A South Korean study by Lee, *et al*<sup>12</sup> reported that older patients, a higher incidence of previous MI, and previous PCI were more frequent in the procedural failure group. Studies which reported a significant number of patients treated with PCI CTO (Hoye, *et al*, European Registry of Chronic Total Occlusion and TOAST-GISE study) did not find statistically significant differences in demographic characteristics between patients with procedural success and procedural failure.<sup>7,13,14</sup>

In our study, there was no correlation between demographic characteristics and procedural failure, except with respect to the incidence of previous myocardial infarction, which was statistically higher in this group of patients. Also, we found that unstable angina pectoris was a predictor of procedural success, which can be partially explained by the fact that symptomatic patients more often have recanalization attempts and eventually successful CTO opening.

Concerning the angiographic details of the CTO recanalization failed procedures, Galassi, *et al* also found that a blunt stump, CTO length > 20 mm, and the presence of severe calcifications were recognized as independent predictors of procedural failure.<sup>14</sup> Also, Rathore, *et al* observed correlations between severe calcification, vessel

**Table IV.** Univariate Analysis of Predictors of Procedural Failure

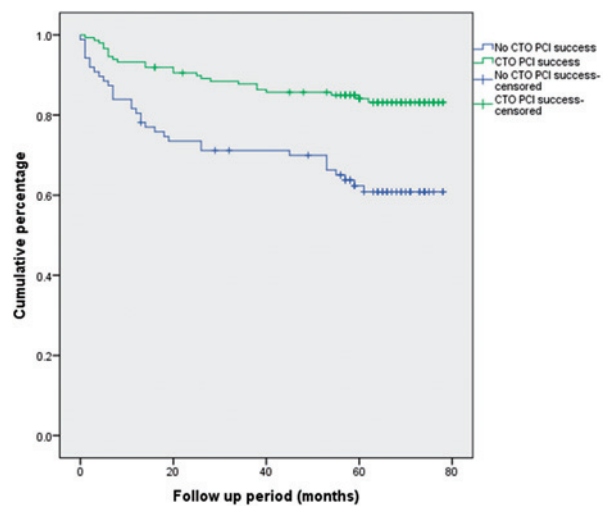
Variable	Odds ratio	95% CI	P value
Male	1.254	0.672-2.340	0.477
Age	0.998	0.973-1.023	0.869
Family history of CAD	1.191	0.733-1.973	0.479
Diabetes mellitus	1.477	0.826-2.642	0.187
Hypertension	1.123	0.616-2.046	0.706
Hypercholesterolemia	1.540	0.870-2.728	0.137
Smoking status			
Smoker	1.375	0.808-2.340	0.240
Ex-Smoker	0.728	0.435-1.218	0.226
Previous MI	0.549	0.326-0.925	0.023
LV EF	1.024	0.978-1.073	0.302
Stable angina	0.933	0.574-1.516	0.780
Unstable angina	3.240	1.600-6.559	0.001
Previous CABG	1.271	0.574-2.814	0.554
Previous PCI			
Same artery	1.184	0.547-2.562	0.668
Other artery	1.068	0.599-1.906	0.823
No. of diseased vessels			
1	0.930	0.577-1.500	0.767
2	1.056	0.642-1.737	0.830
3	1.036	0.562-1.911	0.909
Concomitant therapy			
Beta-blocker	0.491	0.137-1.763	0.276
ACE inhibitor and/or			
ARB	1.062	0.224-5.024	0.940
Statin	0.656	0.138-3.134	0.598
Nitrate	0.607	0.128-2.880	0.530
DAPT	-	-	0.836
OAT	3.049	0.646-14.401	0.159
CTO			
RCA	0.774	0.481-1.247	0.293
LAD	1.336	0.780-2.298	0.291
Cx	1.033	0.592-1.802	0.909
Occlusion duration	0.998	0.992-1.004	0.507
CTO vessel diameter	0.856	0.488-1.500	0.587
CTO length			
≤ 10 mm	1.580	0.805-3.100	0.183
10-20 mm	1.857	1.038-3.321	0.037
≥ 20 mm	0.474	0.228-0.781	0.003
Tortuosity	0.390	0.237-0.640	0.000
Calcification			
Mild	0.520	0.312-0.865	0.012
Moderate	0.214	0.056-0.825	0.025
Severe	0.125	0.035-0.450	0.001
Stump morphology			
Blunt	0.154	0.090-0.263	0.000
Tapered	6.085	3.603-10.278	0.000
Side branch	0.498	0.301-0.793	0.004
In-stent CTO	2.750	0.766-9.880	0.121
CTO localization			
Ostial	2.026	0.783-5.241	0.145
Proximal	0.510	0.509-1.398	0.510
Medial	0.994	0.616-1.605	0.980
Distal	0.914	0.471-1.774	0.790
Technical approach			
Anterograde	0.311	0.088-1.101	0.070
Retrograde	3.212	0.908-11.362	0.070
Number of wires per lesion	1.114	0.844-1.471	0.446
Fluoroscopic time	1.011	0.998-1.024	0.094
Contrast volume	1.002	1.001-1.004	0.009

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; and OAT, oral anticoagulant therapy.

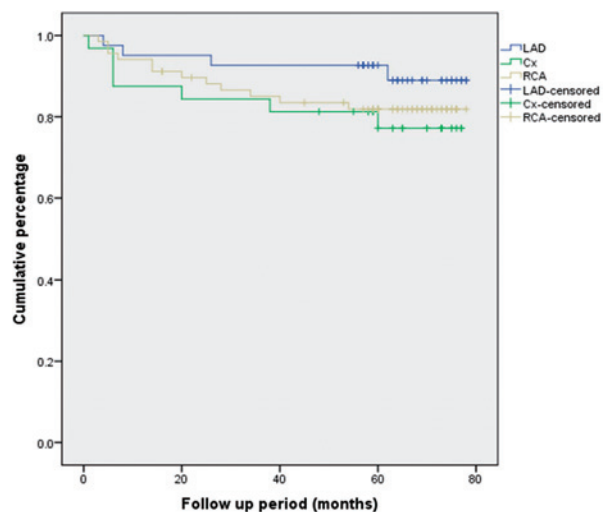
**Table V.** Major Adverse Cardiovascular Events

MACE (n (%))	No of patients (n = 235)	Procedure Successful (n = 148)	Procedure Failed (n = 87)	P value
Death	34 (14.5)	16 (10.8)	18 (20.7)	0.038
CV death	24 (10.2)	11 (7.4)	13 (14.9)	0.066
MI	2 (0.9)	2 (2.3)	0 (0)	0.134
TVR	31 (13.2)	13 (8.8)	18 (20.7)	0.009
PCI	24 (10.2)	11 (7.4)	13 (14.9)	0.066
CABG	7 (3)	2 (1.4)	5 (5.7)	0.05
Total MACE	57 (24.3)	24 (16.2)	33 (37.9)	0.001

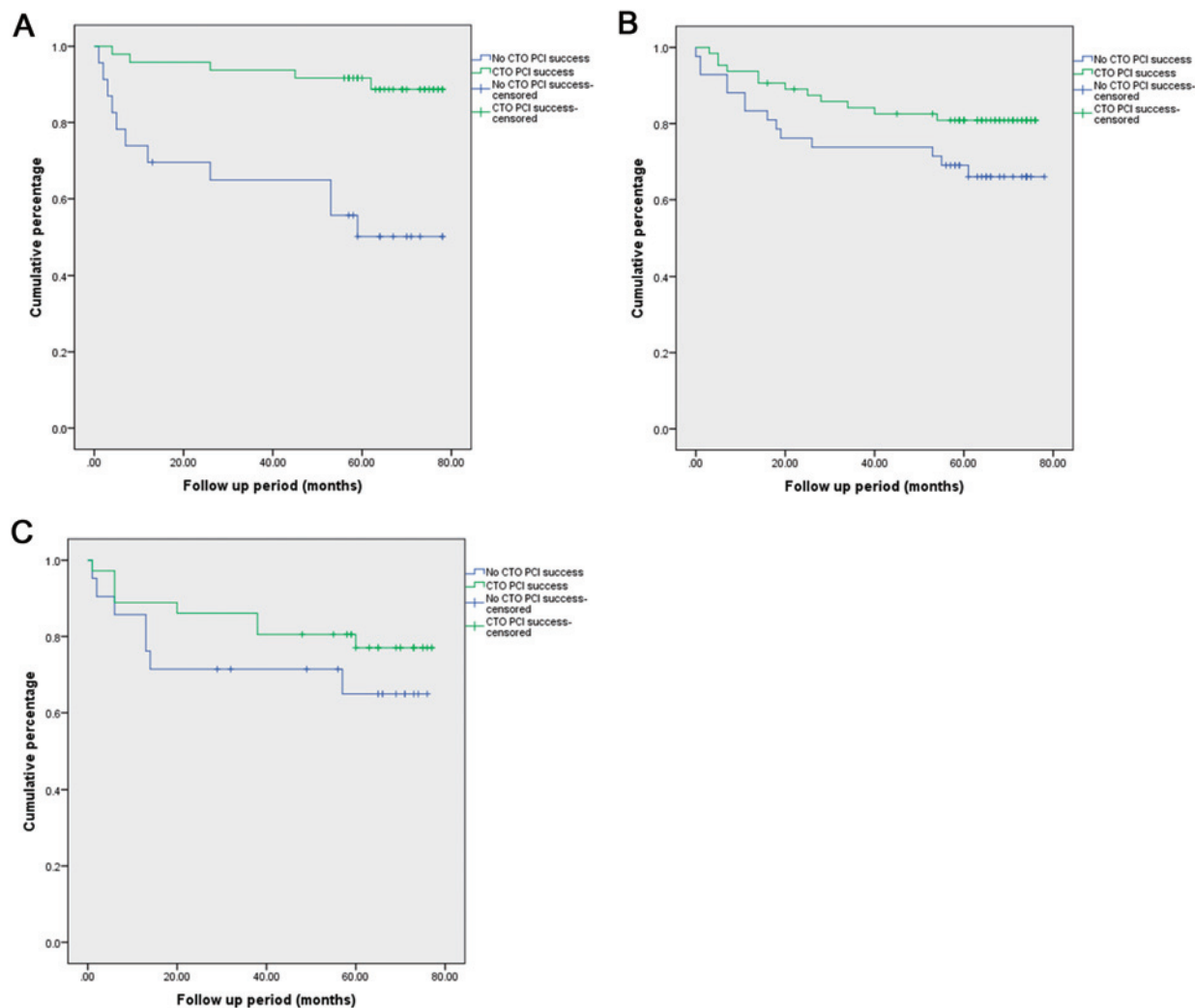
MACE indicates major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting.



**Figure 1.** Survival without MACE. Kaplan-Meier curves showing event-free survival from MACE. The P values were calculated using the log-rank test. Log rank 15.247, P < 0.001.



**Figure 2.** Survival without MACE according to the treated coronary artery. Kaplan-Meier curves showing event-free survival from MACE according to the treated coronary artery. The P values were calculated using the log-rank test. Log rank 2.098, P = 0.35.



**Figure 3.** A: Survival without MACE in patients with total chronic occlusion (CTO) of the left anterior descending coronary artery (LAD). Kaplan-Meier curves showing event-free survival from MACE - percutaneous coronary intervention (PCI) success when compared to patients with CTO-PCI failure. The  $P$  values were calculated using the log-rank test. Log rank 14.638,  $P < 0.001$ . B: Survival without MACE in patients with total chronic occlusion (CTO) of the right coronary artery (RCA). Kaplan-Meier curves showing event-free survival from MACE - percutaneous coronary intervention (PCI) success when compared to patients with CTO-PCI failure. The  $P$  values were calculated using the log-rank test. Log rank 2.850,  $P = 0.091$ . C: Survival without MACE in patients with total chronic occlusion (CTO) of the left circumflex coronary artery (LCx). Kaplan-Meier curves showing event-free survival from MACE-percutaneous coronary intervention (PCI) success when compared to patients with CTO-PCI failure. The  $P$  values were calculated using the log-rank test. Log rank 1.149,  $P = 0.284$ .

tortuosity, and side branch origin at the CTO proximal cap, with procedural failure.<sup>15)</sup> Similarly, our study revealed that after multivariate analysis, calcifications, tortuosity, and blunt stump morphology were independent predictors of procedural failure.

The rate of CTO PCI procedural success in our study was 62.3%. According to the meta-analysis of 13 observational studies, success was achieved in 51 to 74% of CTO recanalization procedures.<sup>16)</sup> However, over the last several years, significant progress in technology, materials, techniques, and operator experience in PCI CTO improved procedural success to almost 90%, and more.<sup>17-22)</sup>

Regarding mortality, a report from the UK Central Cardiac Database showed that successful CTO intervention was associated with improved long-term survival.

Furthermore, this improvement was most pronounced in the group of patients with complete revascularization.<sup>10)</sup> They also found no evidence that the location of the occluded vessel was associated with differences in mortality outcomes. This is in concordance with our results which demonstrated a worse outcome in patients with procedural failure.

Our study showed that all-cause mortality was significantly reduced with successful recanalization of CTO. In some previous studies, successful percutaneous revascularization of a CTO led to a significantly improved survival rate and a reduction in major adverse events at 5 years.<sup>13)</sup> On the other hand, Lee, *et al* did not find a significant relation regarding all-cause mortality between successful and failed CTO recanalization.<sup>23)</sup> The explanations

they proposed included both the low rate of serious complications and the high rate of CABG in the failed PCI group.<sup>24)</sup>

This study also observed significantly better MACE free survival overall in the group of patients with successful treatment of CTO, particularly in patients with a chronically occluded LAD. Possible explanations for the clinical benefit of CTO revascularization survival may include an improvement in LV function in patients with viable myocardium, prevention or slowdown of ventricular remodeling, a decrease in electrical instability, associated risk of fatal arrhythmic events, and increased tolerance of future coronary occlusion events.<sup>25-29)</sup>

**Study limitations:** This was an observational and retrospective study unpowered to evaluate clinical outcome in terms of major cardiovascular events between CTO successful and failed procedures. The major limitation refers to the moderate procedural success of the procedures performed earlier, but still reflecting the worldwide clinical success of CTO recanalization. From one perspective, this time period allows for the evaluation of long-term follow-up and survival, but it suffers from improved technological aspects of CTO procedures and an angiographic successful rate that was significantly improved in the last years. Also, long-term follow-up increases the number of patients lost in the follow-up.

### Conclusion

Our study emphasizes the importance of CTO recanalization in improving long-term outcome, including all-cause and CV mortality, particularly in patients with chronically occluded LAD. In addition, the moderate procedural success of our study in previous years indirectly supports new technological refinements of the procedure that might more easily overcome independent predictors of procedural failure (long, tortuous, calcified lesions with blunt stump), increase the success rate of the procedure, and consequently improve the clinical long-term outcome.

### Disclosures

**Conflicts of interest:** None declared.

### References

1. Fefer P, Knudtson ML, Cheema AN, *et al.* Current perspectives on coronary chronic total occlusions, The Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012; 59: 991-7.
2. Råmunddal T, Hoebers LP, Henriques JP, *et al.* Chronic Total Occlusions in Sweden - A Report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *PLoS One* 2014; 9: e103850.
3. Opolski MP, Ó Hartaigh B, Berman DS, *et al.* Current trends in patients with chronic total occlusions undergoing coronary CT angiography. *Heart* 2015; 101: 1212-8.
4. Suero JA, Marso SP, Jones PG, *et al.* Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol* 2001; 38: 409-14.
5. Mehran R, Claessen BE, Godino C, *et al.* Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv* 2011; 4: 952-61.
6. Melchior JP, Doriot PA, Chatelain P, *et al.* Improvement of left ventricular contraction and relaxation synchronism after recanalization of chronic total coronary occlusion by angioplasty. *J Am Coll Cardiol* 1987; 9: 763-8.
7. Olivari Z, Rubartelli P, Piscione F, *et al.* TOAST-GISE Investigators. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). *J Am Coll Cardiol* 2003; 41: 1672-8.
8. Godino C, Bassanelli G, Economou FI, *et al.* Predictors of cardiac death in patients with coronary chronic total occlusion not revascularized by PCI. *Int J Cardiol* 2013; 168: 1402-9.
9. Arslan U, Balcioglu AS, Timurkaynak T, Cengel A. The clinical outcomes of percutaneous coronary intervention in chronic total coronary occlusion. *Int Heart J* 2006; 47: 811-9.
10. George S, Cockburn J, Clayton TC, *et al.* British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research. Long-term follow-up of elective chronic total coronary occlusion angioplasty - Analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol* 2014; 64: 235-43.
11. Prasad A, Rihal C, Lennon R, Wiste H, Singh M, Holmes D. Trends in outcomes after percutaneous coronary intervention for chronic total occlusion: A 25-year experience from the Mayo clinic. *J Am Coll Cardiol* 2007; 49: 1611-8.
12. Lee SW, Lee JY, Park DW, *et al.* Long-term clinical outcomes off unsuccessful revascularization with drug-eluting stents of true chronic total occlusion. *Catheter Cardiovasc Interv* 2011; 78: 346-53.
13. Hoyer A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992-2002. *Eur Heart J* 2005; 26: 2630-6.
14. Galassi AR, Tomasello SD, Reifart N, *et al.* In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *Eurointervention* 2011; 7: 472-9.
15. Rathore S, Matsuo H, Terashima M, *et al.* Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008. *JACC Cardiovasc Interv* 2009; 2: 489-97.
16. Yoyal D, Afilalo J, Rinfret S. Effectiveness of recanalisation of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 2010; 160: 179-87.
17. Saito S. Progress in angioplasty for chronic total occlusions again. *Catheter Cardiovasc Interv* 2010; 76: 850-1.
18. Godino C, Sharp AS, Carlino M, Colombo A. Crossing CTOs - the tips, tricks, and specialist kit that can mean the difference between success and failure. *Catheter Cardiovasc Interv* 2009; 74: 1019-46.
19. Boden WE, O'Rourke RA, Teo KK, *et al.* COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; 356: 1503-16.
20. Stojkovic S, Sianos G, Katoh O, *et al.* Efficacy, safety, and long-term follow-up of retrograde approach for CTO recanalization: Initial (Belgrade) experience with international proctorship. *J Interv Cardiol* 2012; 25: 540-8.
21. Huang Z, Zhang B, Chai W, *et al.* Usefulness and safety of a novel modification of the retrograde approach for the long tortuous chronic total occlusion of coronary arteries. *Int Heart J* 2017; 58: 351-6.
22. Sekiguchi M, Taguchi T, Miyajima A, Hasegawa S, Yamazaki M, Kurabayashi M. A novel wiring technique to insert a retrograde guidewire directly into the antegrade guiding catheter at the ascending aorta for retrograde percutaneous recanalization

- of an ostial coronary total occlusion. *Int Heart J* 2016; 57: 503-6.
23. Lee PH, Lee SW, Park HS, *et al.* Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. *JACC Cardiovasc Interv* 2016; 9: 530-8.
  24. Usui E, Lee T, Murai T, *et al.* Efficacy of multidetector computed tomography to predict periprocedural myocardial injury after percutaneous coronary intervention for chronic total occlusion. *Int Heart J* 2017; 58: 16-23.
  25. Hochman JS, Lamas GA, Buller CE, *et al*; Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006; 355: 2395-407.
  26. Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circulation* 1987; 75: 229-306.
  27. White HD, Braunwald E. Applying the open artery theory: use of predictive survival markers. *Eur Heart J* 1998; 19: 1132-9.
  28. Silva JC, Rochitte CE, Junior JS, *et al.* Late coronary artery recanalization effect on left ventricular remodelling and contractility by magnetic resonance imaging. *Eur Heart J* 2005; 26: 36-43.
  29. Adachi Y, Sakakura K, Wada H, *et al.* Determinants of left ventricular systolic function improvement following coronary artery revascularization in heart failure patients with reduced ejection fraction (HFrEF). *Int Heart J* 2016; 57: 565-72.