In-hospital Outcomes of Attempting More Than One Chronic Total Coronary Occlusion Through Percutaneous Intervention During the Same Procedure

Peter Tajti, MD[a,b], Khaldoon Alaswad, MD[c], Dimitri Karmpaliotis, MD, PhD[d], Farouc A. Jaffer, MD, PhD[e], Robert W. Yeh, MD[f], Mitul Patel, MD[g], Ehtisham Mahmud, MD[g], James W. Choi, MD[h], M. Nicholas Burke, MD[a], Anthony H. Doing, MD[i], Catalin Toma, MD[j], Barry Uretsky, MD[k], Elizabeth Holper, MD[l], R. Michael Wyman, MD[m], David E. Kandzari, MD[n], Santiago Garcia, MD[o], Oleg Krestyaninov, MD[p], Dmitrii Khelimskii, MD[p], Michalis Koutouzis, MD[q], Ioannis Tsiafoutis, MD[q], Wissam Jaber, MD[r], Habib Samady, MD[r], Jeffrey W. Moses, MD[d], Nicholas J. Lembo, MD[d], Manish Parikh, MD[d], Ajay J. Kirtane, MD[d], Ziad A. Ali, MD[d], Darshan Doshi, MD[d], Iosif Xenogiannis, MD[a], Bavana V. Rangan, BDS, MPH[s], Imre Ungi, MD, PhD[b], Subhash Banerjee, MD[s], and Emmanouil S. Brilakis, MD, PhD[a,*]

The frequency and outcomes of patients who underwent chronic total occlusion (CTO) percutaneous coronary intervention (PCI) of more than one CTO during the same procedure have received limited study. We compared the clinical and angiographic characteristics and procedural outcomes of patients who underwent treatment of single versus >1 CTOs during the same procedure in 20 centers from the United States, Europe, and Russia. A total of 2,955 patients were included: mean age was 65 ± 10 years and 85% were men with high prevalence of previous myocardial infarction (46%), and previous coronary artery bypass graft surgery (33%). More than one CTO lesions were attempted during the same procedure in 58 patients (2.0%) and 70% of them were located in different major epicardial arteries. Compared with patients who underwent PCI of a single CTO, those who underwent PCI of >1 CTOs during the same procedure had similar J-CTO (2.4 ± 1.3 vs 2.5 ± 1.3, p = 0.579) and Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (1.5 ± 1.2 vs 1.3 ± 1.0 p = 0.147) scores. The multi-CTO PCI group had similar technical success (86% vs 87%, p = 0.633), but higher risk of in-hospital major complications (10.3% vs 2.7%, p = 0.005), and consequently numerically lower procedural success (79% vs 85%, p = 0.197). The multi-CTO PCI group had higher in-hospital mortality (5.2% vs 0.5%, p = 0.005) and stroke (5.2%vs 0.2%, p <0.001), longer procedure duration (162 [117 to 242] vs 122 [80 to 186] minutes, p <0.001) and higher radiation dose (3.6 [2.1 to 6.4] vs 2.9 [1.7 to 4.7] Gray, p = 0.033). In conclusion, staged revascularization may be the preferred approach in patients with >1 CTO lesions requiring revascularization, as treatment during a single procedure was associated with higher risk for periprocedural complications. **(Am J Cardiol 2018;122:381–387)**

Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) can be challenging, but can also provide clinical benefits.[1–6] Some patients have >1 CTO lesions that require revascularization. Whether >1 CTO lesions should be attempted during the same procedure has not been systematically studied. We sought to examine the frequency and procedural outcomes of PCI of >1 CTOs during the same procedure in a multicenter registry.

[a]Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, Minnesota; [b]University of Szeged, Division of Invasive Cardiology, Second Department of Internal Medicine and Cardiology Center, Szeged, Hungary; [c]Henry Ford Hospital, Detroit, Michigan; [d]Columbia University, New York, New York; [e]Massachusetts General Hospital, Boston, Massachusetts; [f]Beth Israel Deaconess Medical Center, Boston, Massachusetts; [g]VA San Diego Healthcare System and University of California San Diego, La Jolla, California; [h]Baylor Heart and Vascular Hospital, Dallas, Texas; [i]Medical Center of the Rockies, Loveland, Colorado; [j]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [k]VA Central Arkansas Healthcare System, Little Rock, Arkansas; [l]The Heart Hospital Baylor Plano, Plano, Texas; [m]Torrance Memorial Medical Center, Torrance, California; [n]Piedmont Heart Institute, Atlanta, Georgia; [o]VA Minneapolis Healthcare System and University of Minnesota, Minneapolis, Minnesota; [p]Meshalkin Siberian Federal Biomedical Research Center, Ministry of Health of Russian Federation, Novosibirsk, Russian Federation; [q]Korgialeneio-Benakeio Hellenic Red Cross General Hospital of Athens, Athens, Greece; [r]Emory University Hospital, Atlanta, Georgia; and [s]VA North Texas Health Care System and University of Texas Southwestern Medical Center, Dallas, Texas. Manuscript received January 9, 2018; revised manuscript received and accepted April 3, 2018.

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*Corresponding author: Tel: (612) 863-4204; fax: (612) 863-6441.

E-mail address: esbrilakis@gmail.com (E.S. Brilakis).

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Methods

We analyzed the clinical, angiographic, and procedural characteristics of 2,955 patients enrolled in the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention, NCT02061436) registry between January 2012 and September 2017 at 18 US, 1 European, and 1 Russian centers. Some centers only enrolled patients during part of the study period due to participation in other studies. The study was approved by the institutional review board of each center.

Coronary CTOs were defined as coronary lesions with thrombolysis in myocardial infarction (TIMI) grade 0 flow of at least 3 months duration. Estimation of the duration of occlusion was clinical, based on the first onset of angina, previous history of myocardial infarction (MI) in the target vessel territory, or comparison with a previous angiogram. Calcification was assessed by angiography as mild (spots), moderate (involving $\leq$50% of the reference lesion diameter), and severe (involving $>$50% of the reference lesion diameter). Moderate proximal vessel tortuosity was defined as the presence of at least 2 bends $>70^{\circ}$ or 1 bend $>90^{\circ}$ and severe tortuosity as 2 bends $>90^{\circ}$ or 1 bend $>120^{\circ}$ in the CTO vessel. Blunt or no stump was defined as lack of tapering or lack of a funnel shape at the proximal cap. Interventional collaterals were defined as collaterals considered amenable to crossing by a guidewire and a microcatheter by the operator. A procedure was defined as "retrograde" if an attempt was made to cross the lesion through a collateral vessel or bypass graft supplying the target vessel distal to the lesion; if not, the procedure was classified as "antegrade-only." Antegrade dissection/re-entry was defined as antegrade PCI during which a guidewire was intentionally introduced into the subintimal space proximal to the lesion, or re-entry into the distal true lumen was attempted after intentional or inadvertent subintimal guidewire crossing.

Technical success was defined as successful CTO revascularization with achievement of $<$30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow. Procedural success was defined as achievement of technical success without any in-hospital major adverse cardiac events (MACEs). In patients in whom $>$1 CTO PCI was attempted, procedural success was defined as technical success in at least one major epicardial vessel without any in-hospital MACE. In-hospital MACE included any of the following adverse events previous to hospital discharge: death, MI, recurrent symptoms requiring urgent repeat target vessel revascularization with PCI or coronary artery bypass graft surgery (CABG), tamponade requiring either pericardiocentesis or surgery, and stroke. MI was defined using the third universal definition of MI (type 4a MI).[7] Major bleeding was defined as bleeding causing reduction in hemoglobin $>$3 g/dl or bleeding requiring transfusion or surgical intervention. The J-CTO score was calculated as described by Morino et al,[8] the PROGRESS CTO score as described by Christopoulos et al,[9] and the PROGRESS CTO Complications score as described by Danek et al.[10]

Categorical variables were expressed as percentages and were compared using Pearson's chi-square test or Fisher's exact test. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range) unless otherwise specified and were compared using the *t* test and 1-way analysis of variance for normally distributed variables; the Wilcoxon rank-sum test, and the Kruskal−Wallis test were applied for nonparametric continuous variables, as appropriate. Multivariable logistic regression was used to examine the association between attempting $>$1 CTO lesions during the same procedure and in-hospital MACE after adjusting for confounding variables selected on the ground of univariable association in the present study ($p < 0.10$). All statistical analyses were performed with JMP 13.0 (SAS Institute, Cary, North Carolina). A 2-sided p value of 0.05 was considered statistically significant.

Results

More than one coronary CTOs were present in 690 of 2,955 patients (23%). More than 1 CTO lesions were attempted in 58 of 2,955 patients (2.0%) during the study period. Three CTOs were attempted in one patient and 2 CTOs in the remaining 57 patients.

As compared with patients who underwent single CTO PCI, those in whom $>$1 CTO lesions were attempted during the index procedure had similar age, cardiac risk factors (smoking, dyslipidemia), history of previous MI, previous PCI, previous CABG, and congestive heart failure, but lower left ventricular ejection fraction, and were less likely to have hypertension and diabetes mellitus (Table 1). They were also less likely to undergo ad hoc CTO PCI and more likely to undergo myocardial viability testing. Amongst patients who had $>$1 CTO, those patients in whom $>$1 CTO PCIs were attempted during the same procedure had fewer comorbidities and were less likely to have had previous CABG as compared with those who underwent single CTO PCI (Supplementary Table 1).

In the overall cohort, the most common CTO target vessel was the right coronary artery (55%), followed by the left anterior descending artery (24%) and the left circumflex (20%). The two study groups had similar occlusion length, J-CTO, and PROGRESS CTO scores and similar prevalence of proximal cap ambiguity, moderate to severe calcification and tortuosity, and interventional collaterals. Previously attempted CTO PCIs, however, were less common in patients from the $>$1 CTO PCI group (Table 2).

Primary and secondary target vessels were mostly located in different epicardial territories (71%), but had similar angiographic characteristics and lesion complexity as described by the J-CTO and PROGRESS-CTO scores. Secondary target vessels, however, were smaller in diameter (Supplementary Table 2).

The technical characteristics of the CTO PCIs are summarized in Table 3. Bilateral injection was used in 70% of all cases, with no difference between the $>$1 and 1 CTO groups (71% vs 70%, $p = 0.852$). At least 1 radial access site was selected in 36%, and femoral approach in 82% of cases overall, with no significant differences between the study groups. However, in the $>$1 CTO PCI group, use of biradial access was significantly higher (21% vs 13%, $p = 0.021$), driven by

Table 1
Baseline clinical characteristic classified according to number of interventions performed in the same procedure

Variable	Overall	>1 chronic total occlusion intervention	Single chronic total occlusion intervention	p value
		n = 58	n = 2897	
Age (years)*	65 ± 10	64 ± 10	65 ± 10	0.722
Men	85%	85%	85%	0.916
Body mass index (kg/m^2)*	31 ± 6	31 ± 7	31 ± 6	0.565
Ad-hoc chronic total occlusion intervention	14%	2%	14%	*0.007*
Coronary artery disease presentation				*0.002*
• Stable angina	64%	51%	64%	
• Acute coronary syndrome	25%	24%	25%	
• Other†	11%	26%	11%	
Canadian Cardiovascular Society Angina Classification				*0.003*
• <2	12%	25%	11%	
• 2≤	88%	75%	89%	
Myocardial viability assessment	25%	39%	25%	*0.012*
Myocardial viability test results				0.604
• Viable	91%	95%	91%	
• Nonviable	4%	0%	5%	
• Indeterminate	4%	5%	4%	
Diabetes mellitus	43%	29%	44%	*0.030*
Dyslipidemia	93%	93%	93%	0.854
Hypertension	90%	79%	90%	*0.005*
Smoker (current)	26%	31%	26%	0.392
Left ventricular ejection fraction (%)*	50 ± 13	45 ± 16	50 ± 13	*0.030*
Family history of coronary artery disease	33%	33%	33%	0.957
Congestive heart failure	31%	36%	30%	0.389
Prior myocardial infarction	46%	47%	46%	0.819
Prior valve procedure	3%	7%	3%	0.086
Prior coronary artery bypass graft surgery	33%	32%	33%	0.850
Prior percutaneous coronary intervention	66%	57%	66%	0.161
Cerebrovascular disease	12%	12%	12%	0.873
Peripheral arterial disease	15%	7%	16%	0.078
Lung disease	14%	20%	14%	0.231
Baseline creatinine (mg/dL)*	1.2 ± 0.9	1.1 ± 0.3	1.2 ± 0.9	0.060

Dyslipidemia was defined as (National Cholesterol Education Program criteria): **(a)** Total cholesterol greater than 200 mg/dL (5.18 mmol/l); or **(b)** LDL greater than or equal to 130 mg/dL (3.37 mmol/l); or, **(c)** HDL less than 40 mg/dL (1.04 mmol/l) **(d)** for patients with known coronary artery disease, treatment is initiated if LDL is greater than 100 mg/dL (2.59 mmol/l), and this qualified as hypercholesterolemia.

Hypertension was defined as: **(a)** History of hypertension diagnosed and treated with medication, diet and/or exercise; **(b)** Prior documentation of blood pressure greater than 140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure greater than 130 mm Hg systolic and/or 80 mm Hg diastolic on at least two occasions for patients with diabetes or chronic kidney disease; **(c)** Currently on pharmacologic therapy for treatment of hypertension.

* Mean ± standard deviation.

† Other includes asymptomatic patients, and patients with atypical angina symptoms.

higher use of 1 femoral and 2 radial access sites (9% vs 2%, p <0.001). The use of bifemoral approach was similar in the two groups (p = 0.899), along with combination of bifemoral and single radial approach (p = 0.261). Three or more access sites were used more frequently in the multiple CTO PCI group (13% vs 6%, p = 0.001).

The procedural outcomes and complications are presented in Table 4. Technical and procedural success rates in patients with >1 attempted CTO lesions was 86% and 79%, respectively, and were numerically lower as compared with patients in whom a CTO lesion was attempted (87% and 85%, p = 0.633 and p = 0.197). Patients with >1 CTO PCI received higher radiation dose, had longer fluoroscopy and procedural time, but received similar contrast volume. Left ventricular assist devices were used more often in the >1 CTO PCI group mostly for prophylaxis as compared with single CTO lesion cases. There were no differences in performing PCI of non-CTO lesions in the single CTO versus >1 CTOs groups (28% vs. 23%, p = 0.289).

The technical success of the second CTO lesion in cases with initial success was 86%, while in cases with initial CTO lesion PCI failure, 'PCI of the second lesion had a success rate of 75% (p = 0.410). As compared with cases in which PCI of the first CTO lesion was successful (n = 50), cases in which PCI of the first CTO failed (n = 8) had lower procedural success (90% vs 13%, p <0.001) along with numerically higher in-hospital MACE (8% vs 25%, p = 0.143).

The overall in-hospital major complication rate was 2.8% (83 patients) and was significantly higher in patients with >1 CTO lesion attempts (10.3% vs 2.7%, p = 0.005) as compared with patients who underwent treatment of a single CTO, mostly driven by higher in-hospital mortality (5.2% vs 0.5%, p = 0.005) and stroke (5.2% vs 0.2%, p <0.001). Three patients in the >1 CTO attempted during

Table 2
Angiographic characteristics of the study chronic total occlusions, classified according to the number of CTO lesions attempted during the same procedure

Variable	Overall	>1 chronic total occlusion intervention	Single chronic total occlusion intervention	p value
		n = 117	n = 2897	
Target coronary vessel				*0.019*
Right	55%	43%	56%	
Circumflex	20%	30%	20%	
Left anterior descending	24%	27%	24%	
Other	1%	0%	1%	
Occlusion length (mm)*	30 (16, 40)	28 (15, 40)	30 (16, 40)	0.151
Vessel diameter (mm)*	3.0 (2.5, 3.0)	3.0 (2.5, 3.0)	3.0 (2.5, 3.0)	0.744
Proximal cap ambiguity	35%	34%	35%	0.898
Side branch at proximal cap	50%	45%	50%	0.268
Blunt stump/no stump	54%	50%	54%	0.466
Interventional collaterals	57%	52%	57%	0.373
Moderate/severe calcification	55%	48%	56%	0.106
Moderate/severe tortuosity	36%	38%	36%	0.619
In-stent restenosis	17%	15%	17%	0.634
Prior failed chronic total occlusion intervention	20%	10%	21%	*0.010*
J-CTO score†	2.5 ± 1.3	2.4 ± 1.3	2.5 ± 1.3	0.579
PROGRESS CTO Score†	1.3 ± 1.0	1.5 ± 1.2	1.3 ± 1.0	0.147
PROGRESS CTO complication score†	3.1 ± 1.9	3.0 ± 1.8	3.1 ± 1.9	0.703

CTO = chronic total occlusion; J = Japan; PROGRESS = Prospective Global Registry of Chronic Total Occlusion Intervention.
* Median (interquartile range).
† Mean ± standard deviation.

the same procedure had a stroke during the hospital stay (2 ischemic strokes and 1 hemorrhagic stroke) and 3 patients died (1 patient had pericardial tamponade leading to cardiogenic shock, 1 patient had a vascular access complication leading to hemorrhagic shock, and 1 patient died due to hemorrhagic stroke). In the >1 CTO PCI group, all major in-hospital complications (n = 6) occurred in patients in whom the CTO target vessels were located in different epicardial territories.

In multivariable analysis, attempting >1 CTO lesions during the same procedure was independently associated with higher incidence of in-hospital MACE (odds ratio [OR] = 7.62, 95% confidence interval [CI] 2.68 to 21.72, p <0.001; Figure 1), along with older age (OR = 1.17, 95%

Table 3
Technical characteristics of chronic total occlusion interventions, classified according to the number of interventions performed during the same procedure

Variable	Overall	>1 chronic total occlusion intervention	Single chronic total occlusion intervention	p Value
		n = 117	n = 2897	
Crossing strategies used				
• Antegrade wire escalation	80%	83%	80%	0.485
• Antegrade dissection and re-entry	32%	26%	31%	0.158
• Retrograde	39%	23%	39%	*0.001*
First crossing strategy				0.484
• Antegrade wire escalation	75%	79%	75%	
• Antegrade dissection and re-entry	9%	6%	9%	
• Retrograde	17%	15%	17%	
Final crossing strategy				0.083
• Antegrade wire escalation	45%	54%	45%	
• Antegrade dissection and re-entry	19%	20%	19%	
• Retrograde	24%	14%	24%	
• None	12%	12%	12%	
Balloon uncrossable lesions	11%	5%	12%	*0.047*
Balloon undilatable lesions	11%	6%	11%	0.335
Access site				
• Radial access	36%	39%	36%	0.418
• Bi-radial access	13%	21%	13%	*0.021*
• Femoral access	82%	83%	82%	0.784
• Bi-femoral access	52%	52%	52%	0.899

Table 4
Procedural characteristics, classified according to number of CTO lesions attempted during the same procedure

Variable	Overall	>1 chronic total occlusion intervention	Single chronic total occlusion intervention	p Value
		n = 58	n = 2897	
Technical success	87%	86%	87%	0.633
Procedural success	85%	79%	85%	0.197
				0.289
Left ventricular assist device use	5%	16%	5%	*0.003*
• Urgent	3%	14%	2%	*<0.001*
• Prophylactic	1%	2%	1%	0.404
Procedural time (min)*	123 (81, 188)	162 (117, 242)	122 (80, 186)	*<0.001*
Fluoroscopy time (min)*	47 (29, 76)	63 (39, 97)	47 (28, 76)	*0.002*
Contrast volume (mL)*	270 (200, 360)	308 (213, 411)	270 (200, 358)	0.077
Patient Air Kerma dose (Gray)*	2.9 (1.7, 4.7)	3.6 (2.1, 6.4)	2.9 (1.7, 4.7)	*0.033*

* Median (interquartile range).

Table 5
Incidence of major in-hospital complications, classified according to number of CTO lesions attempted during the same procedure

Variable	Overall	>1 chronic total occlusion intervention	Single chronic total occlusion intervention	p Value
		n = 58	n = 2897	
In-hospital major adverse cardiovascular events	2.8%	10.3%	2.7%	*0.005*
• Death	0.6%	5.2%	0.5%	*0.005*
• Acute myocardial infraction	1.1%	0.0%	1.1%	1.000
• Emergent re-intervention	0.4%	0.0%	0.4%	1.000
• Stroke	0.3%	5.2%	0.2%	*<0.001*
• Emergent cardiac surgery	0.2%	0.0%	0.2%	1.000
• Pericardiocentesis	0.9%	1.6%	0.8%	0.392
Perforation	4.4%	6.9%	4.4%	0.349
Vascular access complication	1.5%	3.5%	1.4%	0.206
Bleeding	1.2%	3.5%	1.1%	0.150

CI 1.09 to 1.25, p <0.001), peripheral vascular disease (OR = 1.95, 95% CI 1.04 to 3.67, p = 0.038), use of at least 1 radial access site (OR = 2.12, 95% CI 1.24 to 3.71, p = 0.006) and application of the retrograde technique (OR = 4.71, 95% CI 2.47 to 8.99, p <0.001).

Discussion

To the best of our knowledge, this is the first systematic assessment of the success and safety of performing multiple CTO PCIs during the same procedure. We found that patients in whom >1 CTOs were attempted during the same procedure had similar technical success, but higher in-hospital major complication rates as compared with patients in whom PCI was attempted in only one CTO lesion.

PCI of multiple CTO target lesions was attempted infrequently (2.0%, 58 of 2,955 patients) in our registry. As anticipated, nearly none of the multi-CTO PCIs were performed ad hoc, and these patients had lower ejection fraction and were more likely to undergo myocardial viability assessment, likely to help determine the potential benefit of coronary revascularization.

There were no significant differences in the complexity of the coronary anatomy except for previous CTO attempt, which was less common in the multiple CTO PCI group. In addition, in patients who underwent PCI of >1 CTO lesions, the angiographic characteristics of the primary and secondary CTO lesions were similar, although the secondary CTOs had smaller reference vessel diameter.

At dedicated, high-volume centers the success rate of CTO PCI varies between 85% and 90%,[1–4,11] but is lower in all comer registries (54% to 79%).[12–15] In our study procedural outcomes were worse in patients who had >1 CTO lesions attempted during the same procedure, due to high incidence of in-hospital MACE (10.3%), including in-hospital mortality (5.2%) and stroke (5.2%). Moreover, multi-CTO interventions required longer procedure and fluoroscopy time along and higher patient radiation dose. The higher rate of stroke could be in part related to ischemia in multiple myocardial territories or use of left ventricular assist devices and multiple (3 or more) access sites. In patients in whom >1 CTO lesions were attempted, target lesions were located in different epicardial territories in most cases (71%) resulting in major complications in 15% in those cases versus 0% of patients in whom all target CTOs were in the same epicardial territory. Therefore, performing PCI of >1 CTOs might be more favorable when the target CTOs are localized in the same epicardial territory, likely because it places less myocardium at risk for ischemia. Nevertheless, staged PCI should, in most cases, be the preferred approach in patients with 2 or more CTO lesions that require revascularization.

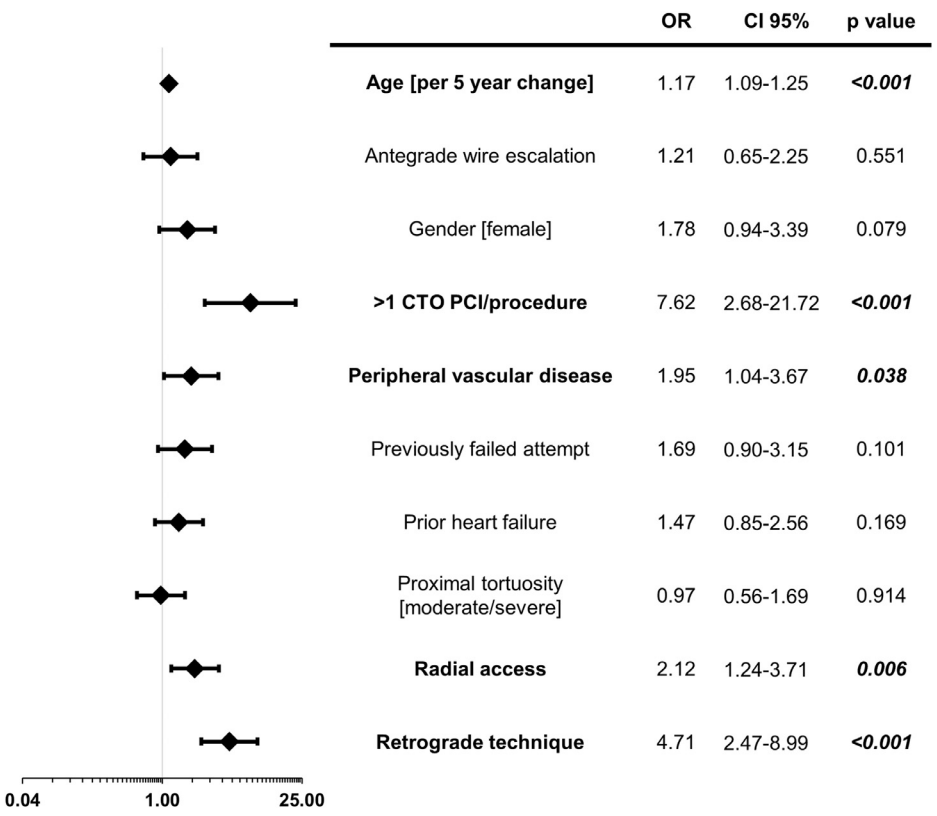

Figure 1. Multivariate analysis for the incidence of in-hospital major adverse cardiac event (MACE).
CI = confidence interval; CTO = chronic total occlusion; OR = odds ratio; PCI = percutaneous coronary intervention.

Our study has several limitations. First, we included only in-hospital outcomes without long-term follow-up; however, the incidence of immediate periprocedural complications was significantly higher in the >1 CTO lesion group, suggesting that long-term outcomes would also likely be worse. Second, there was no core laboratory assessment of the study angiograms or clinical event adjudication. Third, the procedures were performed in dedicated, high-volume CTO centers by experienced operators, limiting the extrapolation to less experienced operators and lower volume centers.

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Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, Minnesota. REDCap is a secure, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.04.021.

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