Journal of the American Heart Association

ORIGINAL RESEARCH

Risk Burden of Coronary Perforation in Chronic Total Occlusion Recanalization: Latin American CTO Registry Analysis

Marcelo Harada Ribeiro, MD; Carlos M. Campos, MD, PhD; Lucio Padilla, MD; Antonio Carlos B. da Silva, MD; João Eduardo T. de Paula, MD; Marco Alcantara, MD; Ricardo Santiago, MD; Franklin Hanna, MD; Franciele R. da Silva, MD; Karlyse C. Belli, PhD; Lorenzo Azzalini, MD, PhD, MSc; Pedro P. de Oliveira, MD, PhD; Gustavo N. Araujo, MD, PhD; Vincenzo Sucato, MD; Kambis Mashayekhi, MD; Alfredo R. Galassi, MD; Alexandre Abizaid, MD, PhD; Alexandre Quadros, MD, PhD

BACKGROUND: Coronary perforation is a life-threatening complication of acute percutaneous coronary intervention (PCI) for chronic total occlusions (CTO), but data on midterm outcomes are limited.

METHODS AND RESULTS: Data from LATAM (Latin American)-CTO Registry (57 centers; 9 countries) were analyzed. We assessed the risk of 30-day, 1-year major adverse cardiac events of coronary perforation using time-to-event and weighted composite end point analysis having CTO PCI without perforation as comparators. Additionally, we studied the independent predictors of perforation in these patients. Of 2054 patients who underwent CTO PCI between 2015 and 2018, the median Multicenter CTO Registry in Japan and Prospective Global Registry for the Study of Chronic Total Occlusion Intervention-Chronic total occlusions scores were 2.0 (1.0–3.0) and 1.0 (0.0–2.0), respectively. The perforation rate was 3.7%, of which 55% were Ellis class 1. After 1-year coronary perforation had higher major adverse cardiac events rates (24.9% versus 13.3%; $P<0.01$). Using weighted composite end point, perforation was associated with increased bleeding and ischemic events at 6 months ($P=0.04$) and 1 year ($P<0.01$). We found as independent predictors associated with coronary perforation during CTO PCI: maximum activated clotting time ($P<0.01$), Multicenter CTO Registry in Japan score ≥2 ($P=0.05$), antegrade knuckle wire ($P=0.04$), and right coronary artery CTO PCI ($P=0.05$).

CONCLUSIONS: Coronary perforation was infrequent and associated with anatomical and procedural complexity, resulting in higher risk of hemorrhagic and ischemic events. Landmark and weighted analysis showed a sustained burden of major events between 6 months and 1 year follow-up.

Key Words: acute myocardial infarction ■ chronic total occlusion ■ coronary perforation ■ percutaneous coronary intervention ■ target vessel revascularization

Chronic total occlusions (CTO) are a frequent finding in daily practice, being present in up to one-third of patients who undergo coronary angiography.[1,2] Successful CTO recanalization is associated with improved ventricular function, a lower incidence of cardiovascular events, and improved cardiopulmonary exercise capacity and quality of life compared to optimal medical therapy.[3–8] Although percutaneous coronary intervention (PCI) for CTO is among the most challenging procedures in interventional cardiology, success rates are increasing due to the development of dedicated equipment, techniques, and growing expertise among surgeons.

Nevertheless, CTO PCI remains associated with higher complication rates than complex non-CTO PCI.[9] Coronary perforation is one of the most feared complications, with an incidence ranging from 1.4%

Correspondence to: Carlos M. Campos, MD, PhD, Department of Interventional Cardiology, Heart Institute (InCor), Universidade de São Paulo (USP), Av Dr Eneas de Carvalho Aguiar, 44, 05403-900 - São Paulo, SP, Brazil. Email: carlosacampos1@gmail.com

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- For the first time an analysis was made in a Latin America Registry regarding clinical impact and midterm outcomes of perforations in patients underwent chronic total occlusion percutaneous coronary intervention.
- Using a weight composite end point and a landmark analysis, we observed worse outcomes at 6 months and at 1 year in the perforation group patients.

What Are the Clinical Implications?

- Coronary perforations during chronic total occlusion percutaneous coronary intervention are far from be considered a benign event, carrying a legacy of worse outcomes.
- Perforation in this group of patients showed worse clinical impact (more bleeding and more ischemic events) on short and midterm follow up, moreover, a strong association with higher anatomical complexity lesion and more aggressive techniques.

Nonstandard Abbreviations and Acronyms

ACT	activated clotting time
CTO	chronic total occlusion
J-CTO	Multicenter CTO Registry in Japan
LATAM	Latin American
MACE	major adverse cardiovascular events
RCA	right coronary artery
TVR	target vessel revascularization
WCE	weighted composite endpoint

to 11.7% in contemporary multicenter registries.[10–12] However, despite being a well-known risk factor for short-term adverse events after CTO PCI, there is little data about the influence of coronary perforation on longer-term outcomes. We sought to assess predictors and clinical impact of coronary perforation during CTO PCI using time-to-event and weighted composite end point (WCE) analysis.

METHODS

Data Availability

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Heart Institute (InCor), Universidade de São Paulo (USP), SP, Brazil at carlosacampos1@gmail.com.

Study Population

The LATAM (Latin American)-CTO registry is an ongoing international initiative to collect data on patients who undergo CTO PCI in Latin America. The registry has been previously described in detail.[13] Patients included in the present analysis were treated at one of the 57 participating centers in Brazil, Argentina, Ecuador, Mexico, Chile, Puerto Rico, Costa Rica, Peru, and Colombia. The inclusion criteria were age >18 years, with at least one CTO PCI attempt. There were no specific requirements regarding CTO PCI volume.

Data Collection

The investigators input CTO PCI data to an online platform available via research electronic data capture (REDCap), a secure, open access web application developed by Vanderbilt University that meets international standards and Brazilian National Agency for Sanitary Surveillance requirements. All investigators received standardized instructions for data entry in REDCap, and clinical, procedural, and angiographic information. Post-procedural clinical outcomes were also collected in the platform. The study was approved by the institutional review board or ethics committee at each participating institution. Because of retrospective enrolment, written informed consent from the patients was waived.

Definitions

CTO was defined as an occlusion in a major coronary artery present for at least 3 months based on clinical or angiographic features, such as previous imaging. CTO PCI was considered technically successful with <30% residual stenosis and thrombolysis in myocardial infarction (MI) flow 3 without significant side branch occlusions. A significant branch supplied the left ventricle and was ≥1.5 mm in diameter.[13]

Standard definitions from the LATAM-CTO registry were used for other clinical, angiographic, procedural, and postoperative details,[13] including J-CTO (Multicenter CTO Registry in Japan)[14] and PROGRESS (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) -CTO[15] scores.

Coronary perforations were classified according to Ellis et al.[16] Ellis class I is defined as “a crater extending outside the lumen only in the absence of linear staining angiographically suggestive of dissection”; Ellis class II involves “pericardial or myocardial blush without a ≥1-mm exit hole” and Ellis class III is considered “frank streaming of contrast through a ≥1-mm exit hole.”

Outcomes

Periprocedural MI was classified according to Society for Cardiovascular Angiography and Interventions[17] criteria[18] as occurring within 72 hours of PCI with a CK-MB ≥10× upper limit normal or CK-MB ≥5× upper limit normal with new pathologic Q-waves in ≥2 contiguous leads (or new persistent left bundle-branch block). Regarding troponin C, the Society for Cardiovascular Angiography and Interventions considers troponin C ≥70× upper limit normal or troponin C ≥35x with new pathologic Q-waves in ≥2 contiguous leads (or new persistent left bundle-branch block) to be a perioperative myocardial injury. Spontaneous MI was defined as the rise and/or fall of cardiac biomarkers (CK-MB or troponin) >72 hours after PCI, in addition to: ECG changes compatible with ischemia, the development of pathological Q-waves, angiographically documented graft or native coronary occlusion, or imaging evidence of a new loss of viable myocardium or a new segmental wall motion abnormality. Major bleeding was defined as a drop >3 g/dL of serum hemoglobin or the need for a blood transfusion as both have demonstrated to be independent predictors of adverse events.[19,20]

Major adverse cardiovascular events (MACE) were defined as a composite of death, myocardial infarction, and target vessel revascularization (TVR). Procedural success was defined as technical success without in-hospital events, such as death, MI, stroke, or tamponade requiring pericardiocentesis or surgery, as well as recurrent symptoms requiring urgent target vessel revascularization with PCI or coronary artery bypass graft surgery.

We also assessed the impact of coronary perforation with WCE analysis.[21,22] In this scoring system, the subject-score is reduced multiplicatively, beginning with a score of 1. A composite of 5 events was considered, with each component assigned a weight based on previous studies: death (1), shock (0.5), MI (0.38), major bleeding (0.3), and target vessel revascularization (0.25), with a maximum weight of 1 per patient.[21–24] In this case, the summary measure was interpreted as the hazard ratio (HR) for health-state adjusted life years. The analysis was based on a modified life table and a Wilcoxon test.[21]

Data Analysis

Continuous variables were expressed as median (interquartile range) and were compared with a Mann–Whitney test. Categorical data were presented as frequencies and were compared using the chi-square test. All tests were 2-sided. The 30-day outcomes were compared using odds ratio (OR) estimate. Long-term outcomes were compared between patients with and without coronary perforation during CTO PCI. Survival curves were derived from Kaplan-Meier estimates and compared using log-rank tests. Multivariable analyses were conducted with a Cox regression model for the occurrence of coronary perforation, using all variables shown in Table 1 and Table 2. The set of variables with a *P*-value ≤0.10 (any LAD territory CTO, any right coronary artery [RCA] territory CTO, severe tortuosity, proximal cap ambiguity, blunt stump at proximal cap, diseased reentry zone, JCTO score, Retrograde Instrumentation, Maximal activated clotting time [ACT], and knuckle wire) in the univariate regression analyses was included in the multivariable regression analyses. Forward selection was used, and the entry and stay criteria were set to 0.05. The data were analyzed using SPSS Statistics (version 23.0.0; IBM, Armonk, NY, USA).

RESULTS

Population

A total of 2054 CTO PCI patients were enrolled in the LATAM registry between January 2015 and October 2019 and were included in the present analysis. Table 1 depicts the baseline clinical characteristics. The mean age was 64 years (57.0–72.0), 78% were male, 37.5% were diabetic, and 11.7% had heart failure. Use of clopidogrel before the procedure was more common in the perforation group (98.1% versus 88.4%, *P*=0.02).

Table 2 shows the procedural characteristics of the study population. The RCA was the most commonly treated vessel (42.3%). Severe calcification was present in 17.8%, severe tortuosity in 48.4%, proximal cap ambiguity in 32.5%, and blunt stump in 47.8%. The median J-CTO score was 2 (1.0–3.0). Overall procedural success was 83.1%.

Coronary perforation occurred in 76 patients (3.7%); 42 (55%) were classified as Ellis class I, 18 (24%) as Ellis class II, and 16 (21%) as Ellis class III. Coronary perforation occurred more frequently during CTO PCI of RCA (55.3% versus 41%, *P*=0.02). Proximal cap ambiguity (56.3% versus 30.7%, *P*<0.01), blunt stump (62% versus 46.4%, *P*=0.01), and diseased reentry zone (41.7% versus 29.8%, *P*=0.04) were more common in patients with than without perforation. J-CTO scores were higher in patients with perforation (2 [1.75–3] versus 2 [1–3], *P*<0.01), but PROGRESS-CTO scores (1 [0–2] versus 1 [0–2], *P*=0.76) did not differ between groups.

Regarding procedural strategy, retrograde instrumentation (35.1% versus 14.7%, *P*<0.01), septal instrumentation (26.3% versus 11.5%, *P*<0.01), and microcatheterization of collateral vessels (34.2% versus 13.9%, *P*<0.01) were more frequent in the perforation group. Any dissection re-entry strategy was associated

Table 1. Baseline Clinical Characteristics

	Overall n=2054	No perforation n=1978	Perforation n=76	*P* value
Medical history				
Male, n (%)	1606 (78.0)	1552 (78.5)	54 (71.1)	0.16
Age, y, median median (IQR)	64.0 (57.0–72.0)	64.0 (57.0–72.0)	64.0 (59.0–74.0)	0.40
BMI, kg/m^2 (IQR)	27.6 (25.2–30.1)	27.7 (25.3–30.2)	27.3 (24.9–29.4)	0.28
Diabetes, n (%)	774 (37.5)	742 (37.9)	32 (42.1)	0.47
Dyslipidemia, n (%)	1483 (71.7)	1428 (73.0)	55 (73.3)	1.00
Hypertension, n (%)	1780 (86.2)	1713 (87.4)	67 (88.2)	1.00
Current smoker, n (%)	373 (18.0)	362 (18.6)	11 (14.5)	0.45
Previous PCI, n (%)	927 (44.9)	889 (48.2)	38 (53.5)	0.40
Previous stroke, n (%)	69 (3.3)	66 (3.6)	3 (4.2)	0.74
Previous CABG, n (%)	288 (13.9)	274 (14.8)	14 (19.7)	0.24
PVD, n (%)	195 (9.3)	184 (10.0)	11 (15,.5)	0.16
Previous MI, n (%)	838 (40.6)	805 (43.8)	33 (46.5)	0.72
Heart failure, n (%)	232 (11.7)	222 (12.1)	10 (14.1)	0.58
Renal failure, n (%)	155 (7.4)	151 (8.2)	4 (5.6)	0.65
Ischemic burden>10%, n (%)	656 (32.0)	631 (31.9)	25 (32.9)	0.90
Anginal class, n (%)				0.30
I/II	936 (63.1)	904 (64.2)	32 (50.8)	
III/IV	535 (36.3)	504 (35.8)	31 (49.2)	
NYHA class, n (%)				0.46
Asymptomatic	1245 (62.9)	1212 (63.4)	43 (58.9)	
I/II	561 (28.3)	540 (28.2)	21 (28.8)	
III/IV	169 (8.6)	160 (8.4)	9 (12.3)	
Medications				
ASA, n (%)	1923 (93.3)	1853 (93.3)	70 (92.1)	0.63
Clopidogrel, n (%)	1340 (90.1)	1287 (88.4)	53 (98.1)	0.02
Ticagrelor, n (%)	126 (8.5)	125 (8.6)	1 (1.9)	0.08
Prasugrel, n (%)	43 (2.9)	43 (3.0)	0 (0.0)	0.40
Coumarin derivatives, n (%)	17 (0.9)	16 (0.8)	1 (1.3)	0.48
NOAC, n (%)	32 (1.5)	32 (1.6)	0 (0.0)	0.63
Beta-blockers, n (%)	1499 (73.2)	1443 (73.0)	56 (73.7)	1.0
Statins, n (%)	1806 (88.1)	1738 (87.9)	68 (89.5)	0.86
ACEI, n (%)	680 (33.1)	657 (33.2)	23 (30.3)	0.62
ARB, n (%)	838 (40.6)	800 (40.4)	38 (50.0)	0.10

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; NOAC, novel oral anticoagulants; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.

with a higher rate of perforation, including antegrade dissection with a knuckle wire technique (26.7% versus 10.4%, *P*<0.01) and retrograde dissection re-entry techniques (4.3% versus 0.3%, *P*<0.01).

The perforation group had longer procedure times (140 [86–214] versus 85 [55–130] minutes, *P*<0.01), a greater contrast volume (310 [210–400] versus 230 [160–300] mL, *P*<0.01), and a higher ACT values (352 [307–400] versus 330 [300–363] seconds, *P*<0.01) during the procedures. Procedural success was less common in the perforation group (52.6% versus 85.3%, *P*<0.01).

Predictors of Coronary Perforation

The independent predictors of coronary perforation are shown in Table 3. A: maximum ACT (OR, 1.003; CI 95% 1.001–1.005; *P*<0.01), J-CTO score ≥2 (OR, 2.98; CI 95% 1.015–8.78; *P*=0.05), antegrade knuckle wire (OR, 2.12; CI 95% 1.046–4.3; *P*=0.04) and RCA CTO PCI (OR, 2.004; CI 95%. 1.016–3.95; *P*=0.05).

Outcomes

At 1 month of follow-up, the perforation group had a higher frequency of hemorrhagic-related events

Table 2. Procedural Characteristics

	Overall n=2054	No perforation n=1978	Perforation n=76	*P* value
Anatomic characteristics				
Left main CTO, n (%)	12 (0.5)	12 (0.6)	0 (0.0)	1.00
Any LAD territory CTO, n (%)	714 (34.7)	696 (35.6)	18 (23.7)	0.04
LAD prox./mid, n (%)	670 (32.6)	653 (33.4)	17 (22.4)	0.05
Any circ. Territory CTO, (%)	451 (21.9)	435(22.2)	16 (21.1)	0.88
Any RCA territory CTO, (%)	843 (42.3)	801 (41.0)	42 (55.3)	0.02
Severe tortuosity, n (%)	944 (48.4)	902 (47.5)	42 (59.2)	0.07
Severe calcification, n (%)	350 (17.8)	335 (17.6)	15 (20.8)	0.67
Proximal cap ambiguity, n (%)	623 (32.5)	583 (30.7)	40 (56.3)	<0.01
Bifurcation CTO, n (%)	610 (31.6)	590 (32.8)	20 (29.4)	0.60
In-stent CTO, n (%)	237 (11.5)	230 (12.0)	7 (9.9)	0.41
Blunt stump at proximal cap, n (%)	921 (47.8)	877 (46.4)	44 (62.0)	0.01
Diseased reentry zone, n (%)	592 (31.8)	562 (29.8)	30 (41.7)	0.04
JCTO score, median (IQR)	2 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.75–3.0)	<0.01
Progress score, median (IQR)	1 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.76
Procedural strategy				
AWE as initial strategy, n (%)	1717 (90.5)	1656 (91.3)	61 (87.1)	0.28
ADR as initial strategy, n (%)	48 (2.3)	47 (2.6)	1 (1.4)	1.0
RWE as initial strategy, n (%)	110 (6.3)	105 (5.8)	5 (7.1)	0.60
RDR as initial strategy, n (%)	9 (0.5)	6 (0.3)	3 (4.3)	<0.01
Retrograde instrumentation, n (%)	311 (15.1)	285 (14.7)	26 (35.1)	<0.01
Septal instrumentation, n (%)	248 (12.0)	228 (11.5)	20 (26.3)	<0.01
Epicardial instrumentation, n (%)	51 (2.5)	48 (2.4)	3 (3.9)	0.43
Retrograde instrumentation trough graft, n (%)	27 (1.3)	23 (1.2)	4 (5.3)	0.02
IVUS guidance, n (%)	334 (19.2)	322 (19.5)	12 (18.8)	1.00
Microcatheter use through collateral channels	300 (14.6)	274 (13.9)	26 (34.2)	<0.01
Rotational atherectomy	67 (3.2)	66 (4.0)	1 (1.6)	0.51
Antegrade knuckle wire, n (%)	221 (10.7)	201 (10.4)	20 (26.7)	<0.01
Retrograde knuckle wire, n (%)	92 (4.5)	80 (4.0)	12 (15.8)	0.06
Procedural duration, min (IQR)	85 (55.0, 130.0)	85.0 (55.0–130.0)	140.0 (86.25–213.8)	<0.01
Contrast media, mL (IQR)	240 (168, 300)	230.0 (160.0–300.0)	310.0 (210.0–400.0)	<0.01
Radiation dose (Air Kerma)	2571.7 (1386.2–4500.0)	1179.5 (652–2262.5)	1632.7 (823.7–2807.0)	0.10
Radiation dose (DAP)	107 227.0 (21 007.0–245 619.0)	12 613.3 (113.5–984 36.5)	7719.0 (120.1–199 067.0)	0.30
Maximal ACT, seconds	367 (330–450)	330.8 (300.0–363.0)	352.5 (307.0–400.0)	<0.01
Iib/IIIA usage	33 (1.6)	32 (1.7)	1 (1.4)	1.00
Procedural results				
Procedural success, n (%)	1707 (83.1)	1667 (85.3)	40 (52.6)	<0.01
Final dissection, n (%)	156 (7.6)	141 (7.2%)	15 (20.3)	<0.01
Donor artery thrombosis, n (%)	14 (0.8)	13 (0.7)	1 (1.3)	0.41
Donor artery dissection, n (%)	27 (1.3)	24 (1.2)	3 (3.9)	0.07
Lateral branch occlusion, n (%)	75 (3.8)	72 (3.7)	3 (4.1)	0.75
Transvenous pacing, n (%)	9 (0.5)	9 (0.5)	0 (0.0)	1.00

ACT indicates activated clotting time; ADR, antegrade dissection re-entry; AWE, antegrade wire escalation; CTO, chronic total occlusion; DAP, dose area product; IQR, interquartile range; IVUS, intravascular ultrasound; LAD, left anterior descending; JCTO, Japanese CTO; RCA, right coronary artery; RDR, retrograde dissection re-entry; and RWE, retrograde wire escalation.

(Figure 1), as well as hemoglobin drop >3 g/dL (OR, 4.65; 95% CI 1.96 –11.02, *P*<0.01) and blood transfusion (OR, 7.96; 95% CI 3.11–20.35; *P*<0.01). Cardiac tamponade occurred in 13.2% of the perforation group (OR, 42.64; 95% CI 15.74–115.5; *P*<0.01) (Figure 1). There was no significant difference in intrahospital

Table 3. Independent Predictors of Coronary Perforation

	OR (95% CI)	*P* value
Maximum ACT	1.003 (1.001–1.005)	0.002
J-CTO score≥2	2.986 (1.015–8.783)	0.047
Antegrade knuckle wire	2.124 (1.046–4.311)	0.037
RCA CTO PCI	2.004 (1.016–3.950)	0.045

ACT indicates activated clotting time; CTO, chronic total occlusion; J-CTO, Japanese CTO; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

mortality between groups (OR, 0.93; 95% CI 0.13–6.91, *P*=0.94).

Figure 2 shows clinical events during the year of follow-up. There was a marked increase in MACE in the perforation group (24.9 versus 13.3%; *P*<0.01) (Figure 2, lower panel). This could be partially explained by a higher incidence of TVR in the perforation group at 1 year (4.6% versus 12.1%, *P*=0.01) and a trend toward higher MI in the perforation group (4.1% versus 9.9%, *P*=0.06). All-cause mortality was 2 times higher in the perforation group, but without reaching statistical significance (3.0% versus 1.5%, HR, 1.99; 95% CI 0.28–14.40; *P*=0.48). A landmark analysis performed between 30 days and 1 year showed that coronary perforation led to a sustained increase in MACE (17.2% versus 9.2%; *P*<0.01; Figure 2, lower panel). Again, MI and TVR were responsible for this higher event rate.

WCE analysis also showed the consequences of coronary perforation (Table 4). Considering only major events (all-cause mortality, MI, TVR, shock, and major bleeding), coronary perforation was associated with adverse outcomes. The difference was evident at 6 months and 1 year of follow-up.

DISCUSSION

The main findings of this study can be summarized as follows: in the LATAM-CTO registry, (1) coronary perforation occurred in 3.7% of the patients and was more frequently Ellis class I (55%); (2) had more complex anatomical features (JCTO score), in RCA CTO PCI, was more frequent when knuckle wire was used and with higher ACT values; (3) led to more bleeding events in short term follow-up; and (4) involved a higher risk of major clinical events in time-to-event and WCE analysis.

Coronary perforation is a feared but relatively common complication of CTO PCI. Its incidence ranges from 1.4% to 11.7% in multicenter registries[10–12,25–27] and is four times more frequent in CTO PCI than non-CTO PCI.[9,26] In the LATAM-CTO registry, we observed coronary perforation in 3.7% of the cases. Most perforations in this study were Ellis class I (55%).

Although previous studies have found that almost half of coronary perforations do not result in adverse outcomes,[28] our findings clearly demonstrate that coronary perforation is associated with poor short and mid-term outcomes. In the first 30 days, patients with this complication experienced more bleeding related events (cardiogenic shock, cardiac tamponade, transfusion, and major bleeding) (Figure 1). Between 30 days and 1 year, coronary perforation impacted ischemic events (MI and TVR; Figure 2, upper panel). Furthermore, according to WCE analysis (MACE plus major bleeding and shock), the negative effects of perforation were evident after 6 months of follow-up.

The higher rates of clinical events in the perforation group can be explained by procedure-related events (bleeding, tamponade, and shock), lower procedural success, and incomplete revascularization (Figure 1 and Table 2). Indeed, bleeding associated with PCI procedures has been associated with a higher risk of mid-term target vessel revascularization and MI.[29] Incomplete revascularization has also been shown to result in a higher rate of MACE.[30,31] Interestingly, in addition to 1-year outcomes, we found that patients with coronary perforation continued to be at risk after the acute phase, both in landmark (Figure 2) and WCE analysis (Table 4).

Of note, this is the first time that WCE analysis has been used to assess the clinical impact of coronary perforation in terms of major (ischemic and

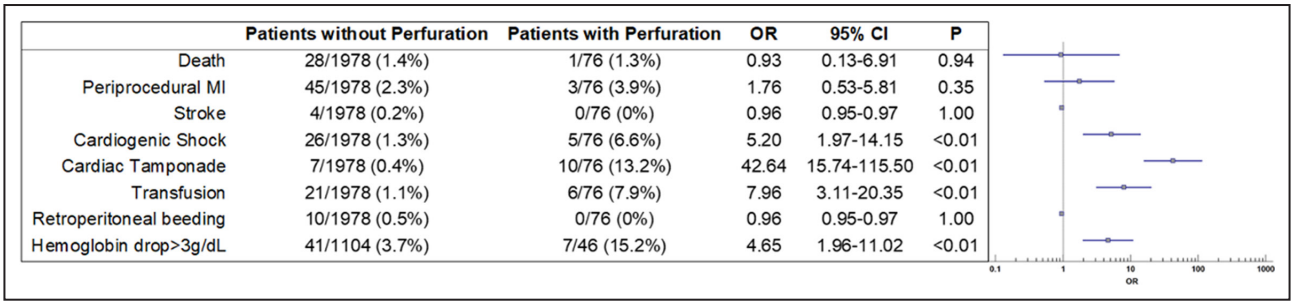
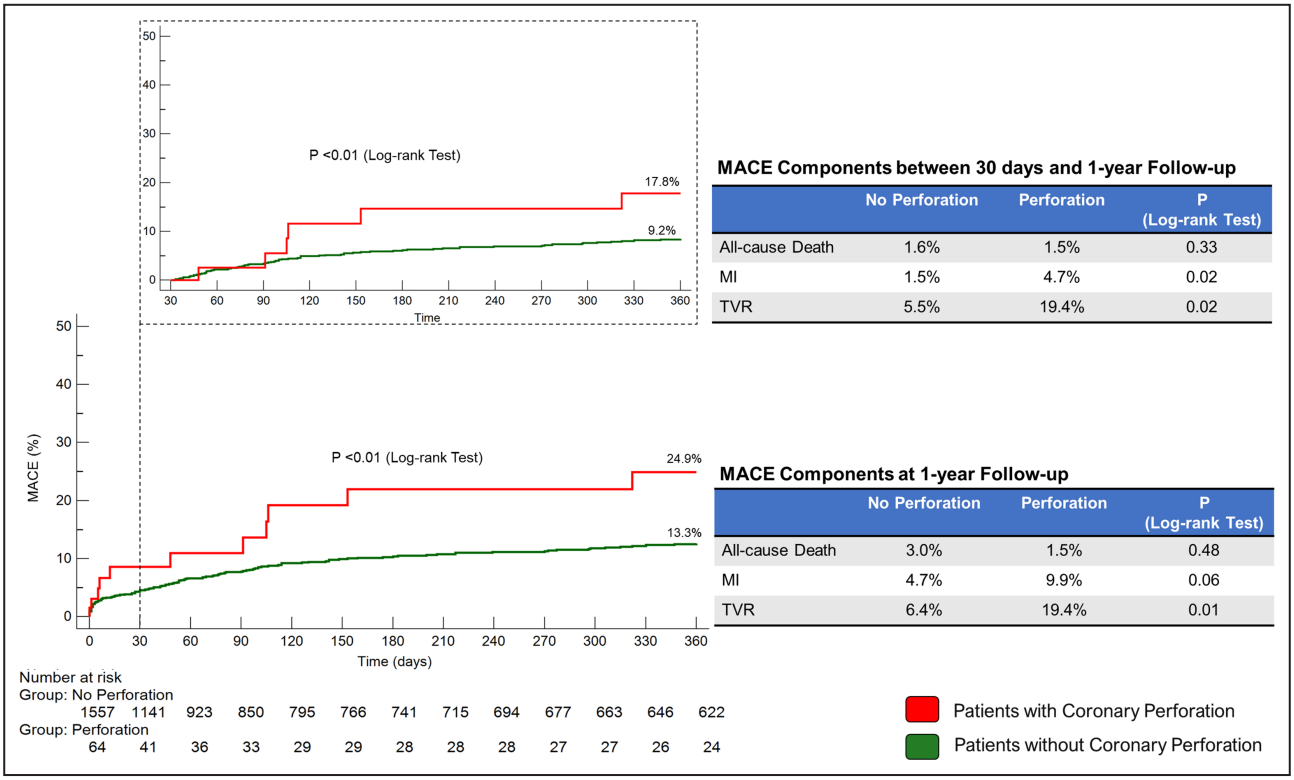


Figure 1. Association of coronary perforation and clinical events at 1 month of follow-up.
MI indicates myocardial infarction; and OR, odds ratio.



MACE Components between 30 days and 1-year Follow-up

	No Perforation	Perforation	P (Log-rank Test)
All-cause Death	1.6%	1.5%	0.33
MI	1.5%	4.7%	0.02
TVR	5.5%	19.4%	0.02

MACE Components at 1-year Follow-up

	No Perforation	Perforation	P (Log-rank Test)
All-cause Death	3.0%	1.5%	0.48
MI	4.7%	9.9%	0.06
TVR	6.4%	19.4%	0.01

Figure 2. Impact of coronary perforation in 1-year clinical events.
MACE indicates major adverse cardiac events (death, myocardial infarction, target vessel revascularization); MI, myocardial infarction; and TVR, target vessel revascularization.

hemorrhagic) events. This reaffirms that patients with coronary perforation are at risk of major events in the long term. WCE adds further additional discriminative power through weighting the components of a composite end point.[21,22] It also allows the incorporation of multiple end points per patient. Traditional time-to-event analysis considers only the first event, and the outcomes are typically counted in a nonhierarchical order. For instance, if repeated revascularization occurs before death, only the first event will affect the Kaplan-Meier survival curve.[23] Importantly, the event weights used in the present study have been previously validated.[21–24]

In our analysis, only angiographic and procedural characteristics could discriminate between the perforation and non-perforation groups. Neither comorbidities, nor ischemic burden, nor symptoms, nor previous medication could identify patients who were more prone to perforation during CTO PCI. However, previous studies have shown that older patients, women, those who have undergone previous coronary artery bypass graft surgery and/or PCI, and those with diabetes are at higher risk of perforation.[12,26] A more recent model developed to predict perforation in CTO PCI found only 2 independently associated clinical characteristics: age (OR, 1.3 per 5-year increase [95% CI 1.1–1.5], $P<0.01$) and ejection fraction (OR, 1.2 per 10% decrease [95% CI 1.1–1.5], $P<0.01$).[32] The remaining independent predictors were procedural related: prior coronary artery bypass graft surgery (OR, 2.0 [95% CI 1.2–3.3], $P<0.01$), occlusion length (OR, 1.2 per 10 mm increase [95% CI 1.1–1.3], $P<0.01$), and heavy calcification (OR, 1.7 [95% CI 1.0–2.7], $P=0.04$).[32]

Several angiographic risk factors were associated with perforation in our analysis: RCA as the CTO PCI target vessel, proximal cap ambiguity or blunt stump, and a diseased reentry zone. Coronary perforation has been commonly associated with RCA as the PCI target vessel. In our analysis, RCA was the target vessel in 55.3% of the CTO cases. In line with our findings, a dedicated core laboratory analysis from the OPEN-CTO registry showed that the majority (69.6%) of coronary perforations were in the RCA.[28] J-CTO scores,

Table 4. Estimates of Survival Free From Weighted Composite Endpoints

	No perforation n=1978	Perforation n=76	Δ	*P* value
Death, MI, TVR, major bleeding, and shock				
30 d	97.4%	98.1%	+0.7%	0.32
180 d	97.1%	95.7%	+1.4%	0.04
1 y	95.4%	90.5%	+4.9%	<0.01

MI indicates myocardial infarction; and TVR, target vessel revascularization.

which summarize greater anatomical complexity, were also higher in perforation cases.

Procedural characteristics, such as retrograde instrumentation, microcatheterization of collateral vessels, retrograde dissection re-entry as an initial strategy, septal instrumentation, and antegrade dissection with a knuckle wire technique were also strongly associated with coronary perforation. In agreement with our findings, a smaller study demonstrated that both retrograde instrumentation and antegrade dissection reentry were independent predictors of coronary perforation.[27] Finally, patients with perforation had longer procedures, received a higher contrast volume, had longer ACT values during the procedure, and had a lower PCI success rate.

We found that perforation is strongly associated with more complex anatomy, as well as more aggressive CTO techniques. Based on the greater patient complexity in contemporary CTO PCI, advanced techniques are essential for success. Since more aggressive techniques are strongly associated with a higher perforation rate, the aggressiveness of the approach must match the experience of the surgeon, and tools to manage this complication, such as coils, covered stents, and pericardiocentesis kits, must be readily available.

The association between higher ACT values and increased risk of perforation deserves closer attention. A pooled analysis of 6 randomized trials of non-CTO PCI[33] (5216 patients) revealed that an ACT between 325 and 350 seconds was associated with fewer ischemic events, whereas higher values were associated with increased bleeding. However, more recent reports did not confirm the latter finding.[34,35] The results of our analysis may provide some explanations: (1) perforations are related to longer procedures, which require more heparin to maintain a target ACT of 300–350 seconds. Heparin reloading is frequently performed with random doses, despite metabolization differences among individuals; (2) CTO PCI demands more aggressive guidewire manipulation, and guidewire micro-perforation is expected in more complex cases. These micro-perforations mostly go unnoticed, although they may become relevant when ACT values are high. Data regarding bleeding and ACT must still be confirmed in other studies in this new era of more complex procedures.

Limitations

Our study must be analyzed in light of certain limitations, the first of which is the observational nature of the study. Although our findings are only hypothesis-generating, real-world data always provide regional trends and insights regarding CTO PCI. Second, the registry is not core laboratory adjudicated. All angiographic characteristics are site-reported, and angiographic appraisal could differ between centers. However, there is a clear relationship between anatomical complexity and coronary perforation, which demonstrates at least a fair angiographic description by the LATAM-CTO registry investigators, reflecting clinical practice. The sustained (after 30 days) risk of patients with perforation may be explained by other factors and not only by the complication itself. It is quite plausible that the higher events rates is explained by a higher atherosclerotic burden (higher anatomical complexity) and the higher TVR rates are related with re-attempts (coronary perforation was strongly associated with unsuccessful CTO PCI). On the other hand, we would like to highlight that patients with coronary perforation had more cardiogenic shock, major bleeding, transfusions. It has been shown that these peri-procedural events have a major impact on long-term follow-up.[36,37]

CONCLUSIONS

In this multicenter real-world study, coronary perforation in CTO PCI was infrequent and was related to greater anatomical complexity. Despite similar clinical characteristics, patients with coronary perforation had an increased risk of both hemorrhagic and ischemic events. Landmark and WCE analysis showed a sustained burden of major events after 30 days and 1 year of follow-up.

ARTICLE INFORMATION

Received November 22, 2021; accepted April 25, 2022.

Affiliations

Heart Institute (InCor), Universidade de São Paulo (USP), São Paulo, Brazil (M.H.R., C.M.C., A.A.); Instituto Prevent Senior, Sao Paulo, São Paulo, Brazil (C.M.C.); Interventional Cardiology Division, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (L.P.); Interventional Cardiology Division, Hospital São José do Avaí, Itaperuna, Rio de Janeiro, Brazil (A.C.d.S.); Interventional Cardiology Division, Instituto Cardiovascular de Linhares UNICOR, Linhares, Espírito Santo, Brazil (J.E.d.P.); Centro Médico Nacional 20 de Noviembre ISSSTE System, Mexico City, México (M.A.); Bayamon Heart & Lung Institute, San Juan, Puerto Rico (R.S.); Clinica Confamiliar, Pereira, Colombia (F.H.); Interventional Cardiology Division, Instituto de Cardiologia do Rio Grande do Sul, Porto Alegre, Brazil (F.R.d.S., K.C.B., P.P.d.O., A.Q.); Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA (L.A.); Imperial Hospital de Caridade, Florianópolis, Santa Catarina, Brazil (G.N.A.); Department of PROMISE, University of Palermo, Palermo, Italy (V.S., A.R.G.); and Division of Cardiology and Angiology II, University Heartcenter Freiburg – Bad KrozingenGermany, (K.M.).

Sources of Funding

None.

Disclosures

Marcelo Harada Ribeiro has received honoraria from Abbott Vascular. Carlos M. Campos has received honoraria from Abbott Vascular, Teleflex, and Terumo. Alexandre Quadros has received honoraria from Boston Sc. and research funds from Boston and Terumo. The remaining authors have no disclosures to report.

REFERENCES

1. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol*. 2012;59:991–997. doi: 10.1016/j.jacc.2011.12.007
2. Galassi AR, Werner GS, Boukhris M, Azzalini L, Mashayekhi K, Carlino M, Avran A, Konstantinidis NV, Grancini L, Bryniarski L, et al. Percutaneous evascularizat of chronic total occlusions: 2019 consensus document from the EuroCTO Club. *EuroIntervention*. 2019;15:198–208. doi: 10.4244/EIJ-D-18-00826
3. Sapontis J, Salisbury AC, Yeh RW, Cohen DJ, Hirai T, Lombardi W, McCabe JM, Karmpaliotis D, Moses J, Nicholson WJ, et al. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO registry (outcomes, patient health status, and efficiency in chronic total occlusion hybrid procedures). *JACC Cardiovasc Interv*. 2017;10:1523–1534. doi: 10.1016/j.jcin.2017.05.065
4. Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR Jr, Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245–253. doi: 10.1016/j.jcin.2014.08.014
5. Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Kim WS, Lee YT, Gwon HC. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv*. 2015;8:271–279. doi: 10.1016/j.jcin.2014.10.010
6. Tomasello SD, Boukhris M, Giubilato S, Marzà F, Garbo R, Contegiacomo G, Marzocchi A, Niccoli G, Gagnor A, Varbella F, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *Eur Heart J*. 2015;36:3189–3198. doi: 10.1093/eurheartj/ehv450
7. Galassi AR, Boukhris M, Toma A, Elhadj ZI, Laroussi L, Gaemperli O, Behnes M, Akin I, Lüscher TF, Neumann FJ, et al. Percutaneous coronary intervention of chronic total occlusions in patients with low left ventricular ejection fraction. *JACC Cardiovasc Interv*. 2017;10:2158–2170. doi: 10.1016/j.jcin.2017.06.058
8. Mashayekhi K, Neuser H, Kraus A, Zimmer M, Dalibor J, Akin I, Werner G, Aurel T, Neumann FJ, Behnes M. Successful percutaneous coronary intervention improves cardiopulmonary exercise capacity in patients with chronic total occlusions. *J Am Coll Cardiol*. 2017;69:1095–1096. doi: 10.1016/j.jacc.2016.12.017
9. Azzalini L, Carlino M, Bellini B, Marini C, Pazzanese V, Toscano E, Gramegna M, Moscardelli S, Bognoni L, Montorfano M. Long-term outcomes of chronic total occlusion recanalization versus percutaneous coronary intervention for complex non-occlusive coronary artery disease. *Am J Cardiol*. 2020;125:182–188. doi: 10.1016/j.amjcard.2019.10.034
10. Salisbury AC, Sapontis J, Grantham JA, Qintar M, Gosch KL, Lombardi W, Karmpaliotis D, Moses J, Cohen DJ, Spertus JA, et al. Outcomes of chronic total occlusion percutaneous coronary intervention in patients with diabetes: insights from the OPEN CTO registry. *JACC Cardiovasc Interv*. 2017;10:2174–2181. doi: 10.1016/j.jcin.2017.08.043
11. Kinnaird T, Gallagher S, Cockburn J, Sirker A, Ludman P, de Belder M, Smith E, Anderson R, Strange J, Mamas M, et al. Procedural success and outcomes with increasing use of enabling strategies for chronic total occlusion intervention. *Circ Cardiovasc Interv*. 2018;11:e006436. doi: 10.1161/CIRCINTERVENTIONS.118.006436
12. Danek BA, Karatasakis A, Tajti P, Sandoval Y, Karmpaliotis D, Alaswad K, Jaffer F, Yeh RW, Kandzari DE, Lembo NJ, et al. Incidence, treatment, and outcomes of coronary perforation during chronic total occlusion percutaneous coronary intervention. *Am J Cardiol*. 2017;120:1285–1292. doi: 10.1016/j.amjcard.2017.07.010
13. Quadros A, Belli KC, Paula JET, Magalhães Campos CAH, Silva ACB, Santiago R, Ribeiro MH, Oliveira PP, Lamelas P, Abelin AP, et al. Chronic total occlusion percutaneous coronary intervention in Latin America. *Catheter Cardiovasc Interv*. 2020;96:1046–1055. doi: 10.1002/ccd.28744
14. Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, Ochiai M, Noguchi Y, Kato K, Shibata Y, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv*. 2011;4:213–221. doi: 10.1016/j.jcin.2010.09.024
15. Christopoulos G, Kandzari DE, Yeh RW, Jaffer FA, Karmpaliotis D, Wyman MR, Alaswad K, Lombardi W, Grantham JA, Moses J, et al. Development and validation of a novel scoring system for predicting technical success of chronic total occlusion percutaneous coronary interventions: the PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) score. *JACC Cardiovasc Interv*. 2016;9:1–9. doi: 10.1016/j.jcin.2015.09.022
16. Ellis SG, Ajluni S, Arnold AZ, Popma JJ, Bittl JA, Eigler NL, Cowley MJ, Raymond RE, Safian RD, Whitlow PL. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. *Circulation*. 1994;90:2725–2730. doi: 10.1161/01.cir.90.6.2725
17. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62:1563–1570. doi: 10.1016/j.jacc.2013.08.720
18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581–1598. doi: 10.1016/j.jacc.2012.08.001
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
20. Leonardi S, Gragnano F, Carrara G, Gargiulo G, Frigoli E, Vranckx P, Di Maio D, Spedicato V, Monda E, Fimiani L, et al. Prognostic implications of declining hemoglobin content in patients hospitalized with acute coronary syndromes. *J Am Coll Cardiol*. 2021;77:375–388. doi: 10.1016/j.jacc.2020.11.046
21. Bakal JA, Westerhout CM, Armstrong PW. Impact of weighted composite compared to traditional composite endpoints for the design of randomized controlled trials. *Stat Methods Med Res*. 2015;24:980–988. doi: 10.1177/0962280211436004
22. Armstrong PW, Westerhout CM, Van de Werf F, Califf RM, Welsh RC, Wilcox RG, Bakal JA. Refining clinical trial composite outcomes: an application to the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial. *Am Heart J*. 2011;161:848–854. doi: 10.1016/j.ahj.2010.12.026
23. Capodanno D, Gargiulo G, Buccheri S, Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, Valgimigli M, et al. Computing methods for composite clinical endpoints in unprotected left main coronary artery revascularization: a post hoc analysis of the DELTA registry. *JACC Cardiovasc Interv*. 2016;9:2280–2288. doi: 10.1016/j.jcin.2016.08.025
24. Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, Lonergan BB, Chan PS. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation*. 2014;130:1254–1261. doi: 10.1161/CIRCULATIONAHA.113.006588
25. Sapontis J, Marso SP, Cohen DJ, Lombardi W, Karmpaliotis D, Moses J, Nicholson WJ, Pershad A, Wyman RM, Spaedy A, et al. The outcomes, patient health status, and efficiency in chronic total occlusion hybrid procedures registry: rationale and design. *Coron Artery Dis*. 2017;28:110–119. doi: 10.1097/MCA.0000000000000439
26. Kinnaird T, Anderson R, Ossei-Gerning N, Cockburn J, Sirker A, Ludman P, deBelder M, Walsh S, Smith E, Hanratty C, et al. Legacy effect of coronary perforation complicating percutaneous coronary intervention for chronic total occlusive disease: an analysis of 26 807 cases from the British Cardiovascular Intervention Society Database. *Circ Cardiovasc Interv*. 2017;10. doi: 10.1161/CIRCINTERVENTIONS.116.004642
27. Azzalini L, Poletti E, Ayoub M, Ojeda S, Zivelonghi C, La Manna A, Bellini B, Lostalo A, Luque A, Venuti G, et al. Coronary artery perforation during chronic total occlusion percutaneous coronary intervention: epidemiology, mechanisms, management, and outcomes. *EuroIntervention*. 2019;15:e804–e811. doi: 10.4244/EIJ-D-19-00282
28. Hirai T, Nicholson WJ, Sapontis J, Salisbury AC, Marso SP, Lombardi W, Karmpaliotis D, Moses J, Pershad A, Wyman RM, et al. A detailed analysis of perforations during chronic total occlusion angioplasty. *JACC Cardiovasc Interv*. 2019;12:1902–1912. doi: 10.1016/j.jcin.2019.05.024
29. Redfors B, Généreux P, Witzenbichler B, Kirtane AJ, McAndrew T, Weisz G, Stuckey TD, Henry TD, Maehara A, Mehran R, et al.

Bleeding severity after percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2018;11:e005542. doi: 10.1161/CIRCINTERVENTIONS.117.005542

30. Généreux P, Campos CM, Yadav M, Palmerini T, Caixeta A, Xu KE, Francese DP, Dangas GD, Mehran R, Leon MB, et al. Reasonable incomplete evascularization after percutaneous coronary intervention: the SYNTAX Revascularisation Index. *EuroIntervention*. 2015;11:634–642. doi: 10.4244/EIJY14M10_05
31. Janella BL, Campos CM, Caixeta A, Almeida BO, Brito FS Jr, Abizaid A, Perin MA. Assessment of long-term mortality in patients with complex coronary artery disease undergoing percutaneous intervention: comparison of multiple anatomical and clinical prognostic risk scores. *EuroIntervention*. 2017;13:1177–1184. doi: 10.4244/EIJ-D-16-00659
32. Hirai T, Grantham JA, Sapontis J, Nicholson WJ, Lombardi W, Karmpaliotis D, Moses J, Nugent K, Gosch KL, Salisbury AC, et al. Development and validation of a prediction model for angiographic perforation during chronic total occlusion percutaneous coronary intervention: OPEN-CLEAN perforation score. *Catheter Cardiovasc Interv*. 2021. doi: 10.1002/ccd.29466
33. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, Topol EJ. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation*. 2001;103:961–966. doi: 10.1161/01.cir.103.7.961
34. Bertrand OF, Rodes-Cabau J, Rinfret S, Larose E, Bagur R, Proulx G, Gleeton O, Costerousse O, De Larochelliere R, Roy L. Impact of final activated clotting time after transradial coronary stenting with maximal antiplatelet therapy. *Am J Cardiol*. 2009;104:1235–1240. doi: 10.1016/j.amjcard.2009.06.036
35. Rajpurohit N, Gulati R, Lennon RJ, Singh M, Rihal CS, Santrach PJ, Donato LJ, Karon BS, Del-Carpio F, Tak T, et al. Relation of activated clotting times during percutaneous coronary intervention to outcomes. *Am J Cardiol*. 2016;117:703–708. doi: 10.1016/j.amjcard.2015.12.003
36. Rao SV, Dai D, Subherwal S, Weintraub WS, Brindis RS, Messenger JC, Lopes RD, Peterson ED. Association between periprocedural bleeding and long-term outcomes following percutaneous coronary intervention in older patients. *JACC Cardiovasc Interv*. 2012;5:958–965. doi: 10.1016/j.jcin.2012.05.010
37. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A. National Institute for Cardiovascular Outcomes R. Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the BCIS database (British Cardiovascular Intervention Society). *JACC Cardiovasc Interv*. 2014;7:1374–1385. doi: 10.1016/j.jcin.2014.06.017