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In-Stent CTO Percutaneous Coronary Intervention

Individual Patient Data Pooled Analysis of 4 Multicenter Registries

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ABSTRACT

OBJECTIVES The authors sought to examine the outcomes of percutaneous coronary intervention (PCI) for in-stent restenosis (ISR) chronic total occlusions (CTOs).

BACKGROUND The outcomes of PCI for ISR CTOs have received limited study.

METHODS The authors examined the clinical and angiographic characteristics and procedural outcomes of 11,961 CTO PCIs performed in 11,728 patients at 107 centers in Europe, North America, Latin America, and Asia between 2012 and 2020, pooling patient-level data from 4 multicenter registries. In-hospital major adverse cardiovascular events (MACE) included death, myocardial infarction, stroke, and tamponade. Long-term MACE were defined as the composite of all-cause death, myocardial infarction, and target vessel revascularization.

RESULTS ISR represented 15% of the CTOs ($n = 1,755$). Patients with ISR CTOs had higher prevalence of diabetes (44% vs. 38%; $p < 0.0001$) and prior coronary artery bypass graft surgery (27% vs. 24%; $p = 0.03$). Mean J-CTO (Multicenter CTO Registry in Japan) score was 2.32 ± 1.27 in the ISR group and 2.22 ± 1.27 in the de novo group ($p = 0.01$). Technical (85% vs. 85%; $p = 0.75$) and procedural (84% vs. 84%; $p = 0.82$) success was similar for ISR and de novo CTOs, as was the incidence of in-hospital MACE (1.7% vs. 2.2%; $p = 0.25$). Antegrade wiring was the most common successful strategy, in 70% of ISR and 60% of de novo CTOs, followed by retrograde crossing (16% vs. 23%) and antegrade dissection and re-entry (15% vs. 16%; $p < 0.0001$). At 12 months, patients with ISR CTOs had a higher incidence of MACE (hazard ratio: 1.31; 95% confidence interval: 1.01 to 1.70; $p = 0.04$).

CONCLUSIONS ISR CTOs represent 15% of all CTO PCIs and can be recanalized with similar success and in-hospital MACE as de novo CTOs. (J Am Coll Cardiol Intv 2021;14:1308–19) © 2021 by the American College of Cardiology Foundation.

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Percutaneous coronary intervention (PCI) of in-stent restenosis (ISR) chronic total occlusions (CTOs) represents 5% to 25% of all CTO PCIs and has been associated with lower success rates in some (1) but not all (2–7) studies. Challenges specific to ISR CTO PCI include inability to maintain an intra-stent track through the stented segment and difficulty re-entering in case of substent wire advancement, poor runoff associated with long stented lengths, and high rates of repeat restenosis (4,8). We examined the outcomes and different practices of ISR CTO PCI at a global level, by combining individual patient-level data from 4 large international multicenter registries.

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METHODS

STUDY POPULATION. We analyzed the clinical, angiographic, and procedural characteristics of 11,961 CTO PCIs performed in 11,728 patients enrolled in 4 multicenter registries, the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; NCT02061436) (6,683 procedures performed between 2012 and 2020 at 34 U.S. and international centers), the LATAM (Latin American) registry (1,700 procedures performed between 2008 and 2020 at 48 centers in 9 Latin American countries), RECHARGE (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium, and United Kingdom; NCT02075372) (1,308 procedures performed between 2013 and 2015 at 18 centers in 4 European countries), and a multicenter registry that included 2,270 cases performed between 2009 and 2017 at 7 participating centers in Italy, Belgium, Japan, Spain, Canada, and the United States. The study was approved by the Institutional Review Board of each site. Patients were divided into 2 groups: in-stent CTOs and de novo CTOs.

DEFINITIONS. Coronary CTOs were defined as 100% coronary stenosis with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 for at least 3 months. Estimation of the duration of occlusion was clinical, on the basis of the first onset of angina, history of myocardial infarction (MI) in the target vessel territory, or comparison with a prior angiogram. In-stent CTOs were defined as occlusions at the stent site and/or at the stent site or within 5 mm proximal or distal to the stent. 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 and 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. Radial access was used to indicate cases with dual radial access or cases with a single access being radial. Technical success was defined as successful CTO revascularization with achievement of <30% residual diameter stenosis within the treated segment and restoration of TIMI flow grade 3 antegrade. Procedural success was defined as the achievement of technical success without any in-hospital major adverse cardiovascular events (MACE), which included any of the following adverse events prior to hospital discharge: death, MI, tamponade requiring either pericardiocentesis or surgery, and stroke. MI was defined using the third universal definition of MI (type 4a MI) (9). The J-CTO (Multicenter CTO Registry in Japan) score was calculated as described by Morino et al. (10) and the PROGRESS-CTO score as described by Christopoulos et al. (11).

One-year MACE was defined as the composite of all-cause death, MI, or target vessel revascularization at 12-month follow-up. Target vessel revascularization was defined as the performance of either PCI or coronary artery bypass surgery to revascularize the target vessel.

STATISTICAL ANALYSIS. Categorical variables are presented as percentages and were compared using the Pearson chi-square test or the Fisher exact test. Continuous variables are presented as mean ± SD in case of normal distribution or as median (interquartile range [IQR]) in case of non-normal distribution and were compared using Student's *t*-test and one-way analysis of variance for normally distributed variables and using the Wilcoxon rank-sum test and the Kruskal-Wallis test for nonparametric continuous variables, as appropriate. Multivariable logistic regression was used to examine the association between ISR versus de novo CTO and technical

ABBREVIATIONS AND ACRONYMS

CTO = chronic total occlusion

IQR = interquartile range

ISR = in-stent restenosis

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics of the Study Patients Classified According to Whether the Target CTO Was In-Stent or De Novo

	ISR CTOs (n = 1,727)	De Novo CTOs (n = 10,001)	p Value
Men	1,378 (82.8)	8,142 (83.5)	0.48
Age (yrs)	65 (58-71)	65 (58-72)	0.10
BMI (kg/m^2)	29.4 (26.1-33.2)	28.7 (25.8-32.3)	**<0.0001**
Diabetes	713 (43.5)	3,641 (37.8)	**<0.0001**
Dyslipidemia	1,436 (87.3)	7,888 (81.6)	**<0.0001**
Hypertension	1,456 (88.5)	8,037 (83.2)	**<0.0001**
Prior MI	903 (57.1)	3,926 (42)	**<0.0001**
Prior CABG	443 (26.5)	2,333 (24)	**0.0275**
LVEF >50%	888 (60.8)	5,402 (61.1)	0.80
Heart failure	319 (25.5)	1,721 (23.1)	0.07
Peripheral artery disease	250 (16.1)	1,262 (13.9)	**0.0227**
Cerebrovascular disease	123 (7.9)	779 (8.6)	0.38
Estimated GFR (ml/min/1.73 m^2)	73 (59-87)	75 (60-90)	**0.0059**
CTO indication			**<0.0001**
Symptom relief	1,025 (73.4)	5,166 (66.6)	
Ischemia reduction	157 (11.3)	1,058 (13.6)	
Reduced ejection fraction	54 (3.9)	346 (4.5)	
Other	64 (4.6)	473 (6.1)	

Values are n (%) or median (interquartile range). The p values in **bold** indicate statistical significance.

CABG = coronary artery bypass grafting; CTO = chronic total occlusion; GFR = glomerular filtration rate; ISR = in-stent restenosis; LVEF = left ventricular ejection fraction, MI = myocardial infarction.

TABLE 2 Baseline Angiographic Characteristics, Classified According to Whether the Target CTO Was In-Stent or De Novo

	ISR CTOs (n = 1,755)	De Novo CTOs (n = 10,206)	p Value
Arterial access (radial)	746 (42.6)	5,065 (49.6)	**<0.0001**
Target vessel			0.29
LAD	450 (26.4)	2,771 (27.8)	
RCA	881 (51.7)	5,197 (52.1)	
LCx	365 (21.5)	1,971 (19.8)	
Other	7 (0.4)	29 (0.3)	
Proximal cap ambiguity	429 (26.8)	3,379 (36.2)	**<0.0001**
Moderate/severe calcification	555 (35.6)	4,219 (48.3)	**<0.0001**
Moderate or severe proximal tortuosity	396 (25.6)	2,338 (26.9)	0.37
Ostial lesion	226 (17.1)	931 (12)	**<0.0001**
Interventional collateral vessels	879 (55.9)	5,746 (62.2)	**<0.0001**
Werner classification of collateral vessels			**<0.0001**
CC 0	257 (22.4)	1,141 (17.6)	
CC 1	612 (53.3)	3,358 (51.8)	
CC 2	279 (24.3)	1,978 (30.5)	
J-CTO score	2.32 ± 1.26	2.22 ± 1.27	**0.0111**
J-CTO score ≥2	1,209 (72.7)	6,909 (69.2)	**0.0048**
PROGRESS-CTO score	1 (0-2)	1 (0-2)	0.74
PROGRESS-CTO ≥2	489 (34.7)	2,784 (34.2)	0.76

Values are n (%), mean ± SD, or median (interquartile range). The p values in **bold** indicate statistical significance.

CC = collateral connection; J-CTO = Multicenter CTO Registry in Japan; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PROGRESS-CTO = Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; RCA = right coronary artery; other abbreviations as in Table 1.

success, after adjusting for confounding variables selected on univariable association ($p < 0.10$). A 2-sided p value < 0.05 was considered to indicate statistical significance. The analysis was performed on a per patient basis for baseline characteristics and procedural outcomes and on a per procedure basis for angiographic parameters and technical aspects of the study procedures. The cumulative incidence of the composite endpoint at 1 year was calculated using Kaplan-Meier estimates and compared using the log-rank test. Although patients could experience more than 1 component of the composite endpoint, each patient was assessed until the occurrence of his or her first event and only once during the analysis for the composite endpoint. All statistical analyses except for the survival analysis were performed using JMP version 13.0 (SAS Institute, Cary, North Carolina). The survival analysis was performed with the survival, survminer, and finalfit R packages using jamovi version 1.2 (https://www.jamovi.org).

RESULTS

PATIENT CHARACTERISTICS. A total of 1,755 ISR CTO PCIs (14.7% of total CTO PCIs) performed in 1,727 patients were included in the present analysis. The baseline characteristics of the study patients are summarized in Table 1. Patients in the ISR group had a higher prevalence of diabetes mellitus (43.5% vs. 37.8%; $p < 0.001$), dyslipidemia, hypertension, and prior MI compared with patients who had de novo CTOs. They also had slightly higher body mass index and higher prevalence of prior coronary artery bypass graft surgery (26.5% vs. 24%; $p = 0.028$) and peripheral artery disease (16.1% vs. 13.9%; $p = 0.02$).

ANGIOGRAPHIC CHARACTERISTICS. The baseline angiographic characteristics of the study lesions are shown in Table 2. Radial access was used more often in the de novo group compared with the in-stent group (50% vs. 43%; $p < 0.001$). Proximal cap ambiguity (26.8% vs. 36%; $p < 0.001$) and moderate to severe calcification (35.6% vs. 48.3%; $p < 0.001$) were more frequent in the de novo CTO group, while ostial occlusion location was more frequent in the ISR CTO group (17.1% vs. 12.0%; $p < 0.001$). Mean J-CTO score was higher in the ISR CTO group (2.32 ± 1.27 vs. 2.22 ± 1.27; $p = 0.01$).

TECHNICAL CHARACTERISTICS AND PROCEDURAL OUTCOMES. The technical aspects of CTO PCI are summarized in Table 3. The retrograde approach (26.2% vs. 36%; $p < 0.001$) and antegrade dissection or re-entry (25.3% vs. 26.4%; $p < 0.001$) were used less often in ISR CTOs compared with de novo lesions, and intravascular imaging (intravascular ultrasound or optical coherence tomography) was used more often (40.5% vs. 32.7%; p < 0.001). Stenting was used less often in the ISR CTO group (80.0% vs. 84.4%; p < 0.001).

Procedural outcomes are summarized in **Table 4**. Technical (84.9% vs. 85.2%; p = 0.75) and procedural (84% vs. 84%; p = 0.82) success and in-hospital MACE rates (1.7% vs. 2.2%; p = 0.25) were similar between ISR and de novo CTOs. Contrast volume was lower in the ISR CTO group (median 215 ml [IQR: 150 to 300 ml] vs. 250 ml [IQR: 180 to 340 ml]; p < 0.001). Technical success of ISR CTO PCI, number of ISR CTOs, in-hospital MACE rate, median J-CTO score, and contrast volume according to year of procedure are shown in **Figure 1**.

DIFFERENCES ACROSS REGISTRIES. There were no significant differences in technical success for ISR CTO PCI among the registries (**Figure 2A**). However, there were differences in various crossing strategies used during the procedure (**Figure 2B**), successful crossing strategies (**Figure 2C**), in-hospital MACE rates (**Figure 2D**), and contrast volume use patterns (**Figure 2E**).

MULTIVARIABLE ANALYSIS. On multivariable analysis, ISR CTO PCI was not independently associated with technical success (odds ratio [OR]: 0.96; 95% confidence interval: 0.81 to 1.14; p = 0.68) (**Figure 3**).

FOLLOW-UP OUTCOMES. Long-term follow-up was available for 5,701 patients (48.6% of the total population). The median duration of follow-up was 306 days (IQR: 57 to 365 days). At 12 months, patients with ISR CTOs had a higher incidence of MACE (hazard ratio: 1.31; 95% confidence interval: 1.01 to 1.70; p = 0.04) (**Central Illustration**) and target vessel revascularization (hazard ratio: 1.34; 95% confidence interval: 1.00 to 1.81; p = 0.05) but similar rates of MI (hazard ratio: 1.50; 95% confidence interval: 0.78 to 2.90; p = 0.23) and death (hazard ratio: 1.30; 95% confidence interval: 0.74 to 2.26; p = 0.36) (**Figure 4**).

DISCUSSION

The present study is a unique cooperation across 4 independent multinational registries and to the best of our knowledge provides the largest published patient cohort comparing the outcomes of PCI in in-stent versus de novo CTOs. The main findings were that ISR CTO PCI: 1) represented 15% of all CTO interventions; 2) had similar success and in-hospital MACE rates compared with PCI of de novo CTOs; 3) was less likely to require use of the retrograde approach and antegrade dissection and re-entry techniques; and 4) was not independently associated with technical success; in addition, 5) patients with ISR CTOs had higher a incidence of MACE and target vessel revascularization during follow-up.

PREVIOUS STUDIES. The prevalence of in-stent CTOs in our study was higher (15%) compared with the

TABLE 3 Technical Characteristics and Outcomes in the Study Procedures, Classified According to Whether the Target CTO Was In-Stent or De Novo

	ISR CTOs (n = 1,755)	De Novo CTOs (n = 10,206)	p Value
Crossing strategies used			
Antegrade wiring	1,480 (84.8)	8,187 (81)	**0.0002**
ADR	439 (25.3)	2,739 (26.4)	**0.0302**
Retrograde	455 (26.2)	3,619 (36)	**<0.0001**
Retrograde wire escalation (% of retrograde)	172 (51.5)	1,284 (45.6)	**0.041**
Retrograde dissection/re-entry (% of retrograde)	138 (41.4)	1,402 (49.9)	**0.0036**
Successful crossing strategy			**<0.0001**
Antegrade wiring	1,042 (69.5)	5,286 (60.8)	
ADR	218 (14.5)	1,402 (16.1)	
Retrograde	239 (15.9)	2,005 (23.1)	
IVUS and/or OCT used	628 (40.5)	2,795 (32.7)	**<0.0001**
CrossBoss	19 (11.5)	832 (8.6)	**0.0001**
Stenting	1,391 (83.5)	8,490 (86.8)	**0.0003**
Number of stents	2 (1-3)	2 (1-3)	0.25
Stent type			0.17
Drug-eluting stent	1,167 (97.4)	6,788 (96.6)	
Bare-metal stent	10 (0.83)	106 (1.5)	
Bioresorbable vascular scaffold	21 (1.8)	136 (1.9)	
Total stent length	64 (38-94)	64 (38-94)	0.10
Technical success	1,489 (84.9)	8,686 (85.2)	0.75

Values are n (%) or median (interquartile range). The p values in **bold** indicate statistical significance.
ADR = antegrade dissection and re-entry; IVUS = intravascular ultrasound; OCT = optical coherence tomography; other abbreviations as in **Table 1**.

TABLE 4 Procedural Outcomes of the Study Patients Classified According to Lesion Type

	ISR CTOs (n = 1,727)	De Novo CTOs (n = 10,001)	p Value
Procedural success	1,446 (83.7)	8,413 (83.9)	0.82
In-hospital MACE	33 (1.9)	248 (2.5)	0.15
Death	3 (0.18)	51 (0.51)	0.0565
Myocardial infarction	14 (0.82)	90 (0.91)	0.72
Stroke	6 (0.35)	23 (0.23)	0.37
Tamponade	13 (0.75)	113 (1.13)	0.16
Fluoroscopy time (min)	40 (24-62)	41 (25-66)	0.07
Procedure time (min)	110 (69-159)	107 (69-159)	0.78
Contrast volume (ml)	215 (150-300)	250 (180-340)	**<0.0001**
Bleeding	3 (0.3)	40 (0.7)	0.09

Values are n (%) or median (interquartile range). The p values in **bold** indicate statistical significance.
MACE = major adverse cardiovascular events; other abbreviations as in **Table 1**.

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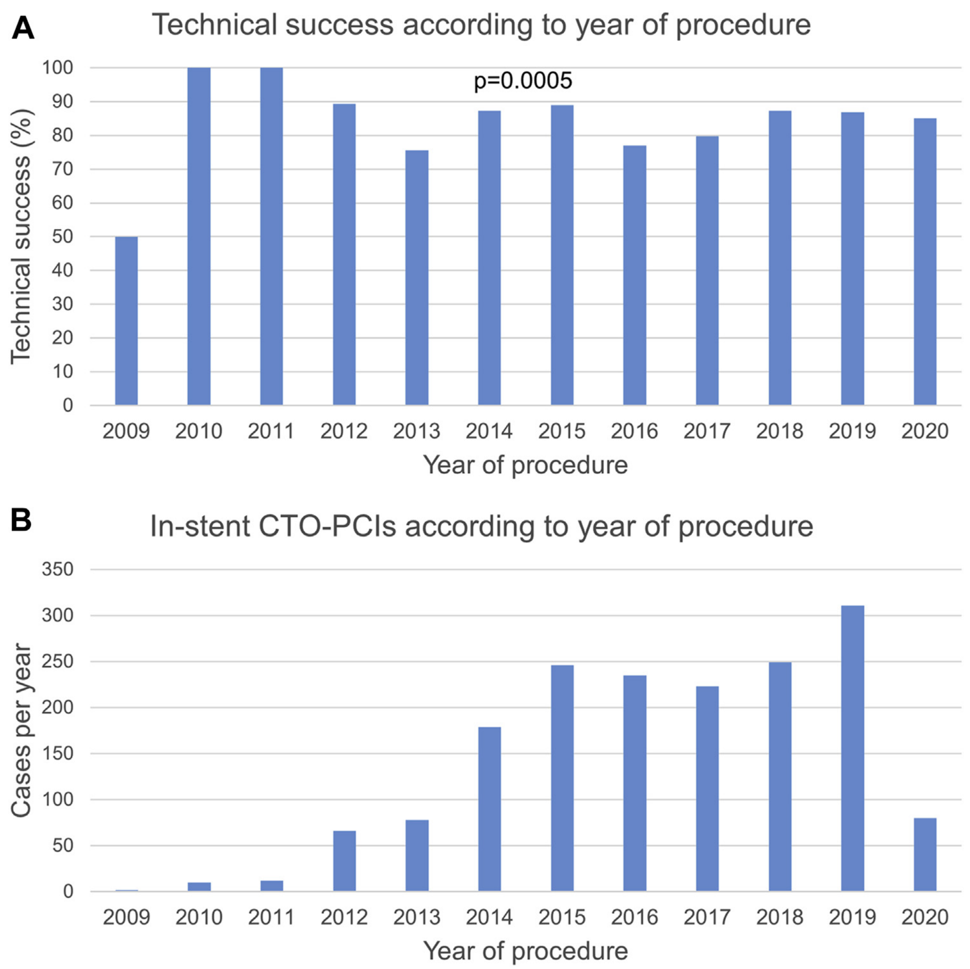
FIGURE 1 Temporal Trends in In-Stent CTO PCI



(A) Technical success of in-stent chronic total occlusion (CTO) percutaneous coronary intervention (PCI) according to year of procedure. **(B)** Number of in-stent CTO PCIs according to year of procedure. **(C)** In-hospital major adverse cardiovascular events (MACE) associated with in-stent CTO PCIs according to year of procedure. **(D)** Median J-CTO (Multicenter CTO Registry in Japan) score of in-stent CTO PCIs according to year of procedure. The median divides the dataset into bottom and top halves. The **bottom line and top line of each box** represent quartiles 1 and 3, respectively. **Whiskers** show the 10th and 90th percentiles. In those cases in which no whisker is visible, the value of the 10th percentile coincides with the value of quartile 1. **(E)** Median contrast volume for in-stent CTO PCIs according to year of procedure. The median divides the dataset into bottom and top halves. The **bottom line and top line of each box** represent quartiles 1 and 3, respectively. **Whiskers** show the 10th and 90th percentiles. In those cases in which no whisker is visible, the value of the 10th or 90th percentile coincides with the value of quartile 1 or quartile 3, respectively.

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overall prevalence of in-stent lesions in the National Cardiovascular Registry (10%) (12). A number of observational studies have compared the outcomes of ISR CTO PCI, including studies whose patients were included in the present analysis (3,4,7). Initial studies, published between 2005 and 2011, by Abdel-Karim et al. (13), Abbas et al. (1), and Werner et al. (14), showed that success rates of ISR CTO PCI were lower compared with PCI of de novo CTOs, likely because of the use of limited equipment and techniques. However, contemporary studies showed no difference in technical success rates between ISR and de novo CTO PCI (3–7,15), as confirmed by our analysis. The high success rates are likely the result of

FIGURE 1 Continued

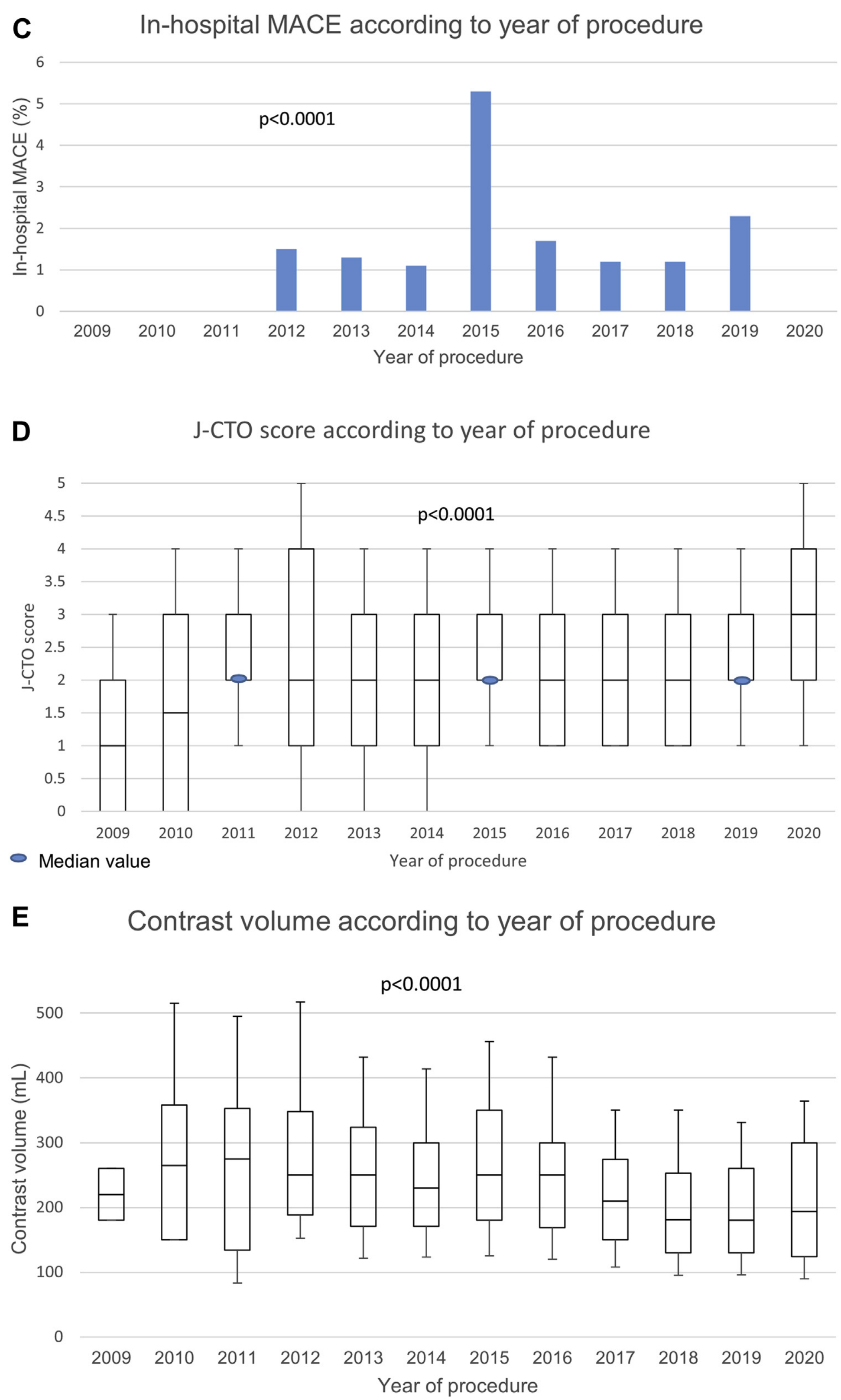
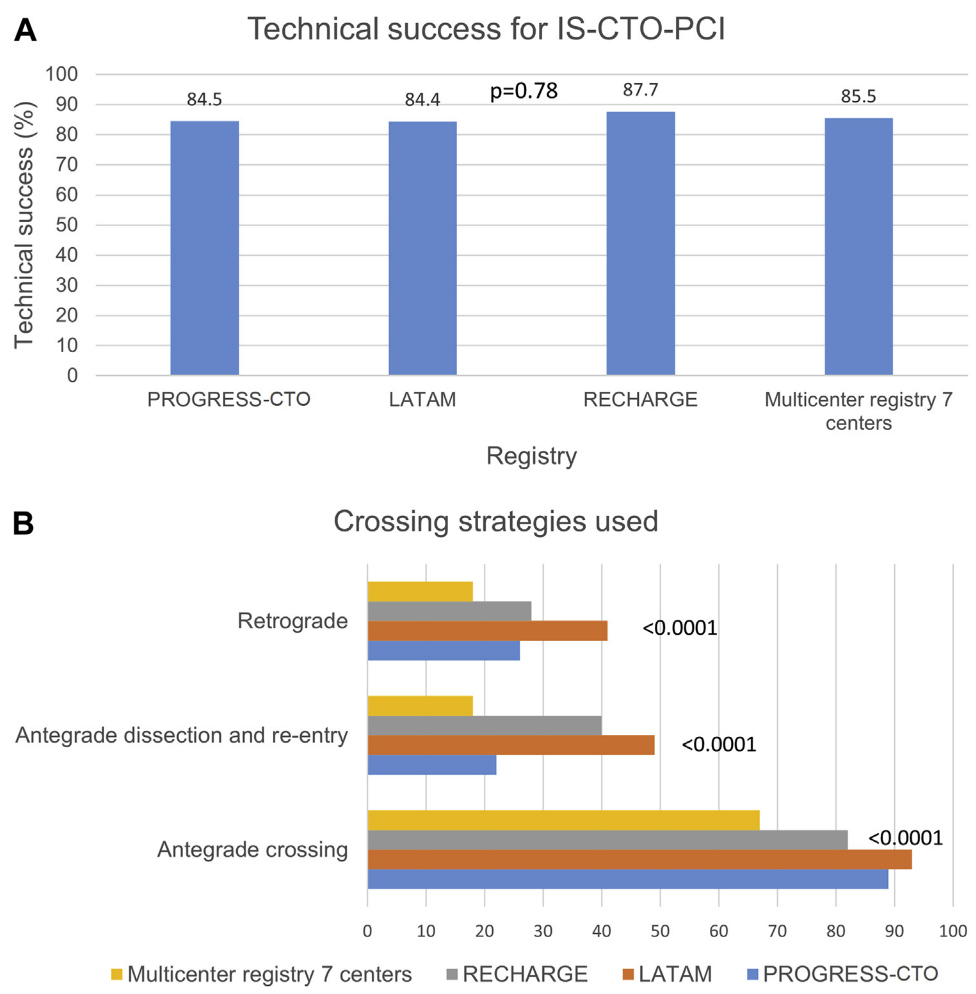


FIGURE 2 **Inter-Registry Differences for IS CTO PCIs**



(A) Technical success of in-stent (IS) CTO PCIs according to registry. **(B)** Crossing strategies of IS CTO PCI according to registry. **(C)** Successful crossing strategy used for IS CTO PCIs according to registry. **(D)** In-hospital MACE associated with IS CTO PCIs according to registry. **(E)** Median contrast volume use associated with IS CTO PCIs according to registry. The median divides the dataset into bottom and top halves. The **bottom line and top line of each box** represent quartiles 1 and 3, respectively. **Whiskers** show the 10th and 90th percentiles. LATAM = Latin American registry; PROGRESS-CTO = Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; RECHARGE = Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium, and United Kingdom; other abbreviations as in Figure 1.

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improved CTO PCI equipment and techniques and increasing operator experience, as suggested by increasing ISR CTO PCI success rates over time.

CLINICAL CHARACTERISTICS. Patients with in-stent CTOs were more likely to have diabetes and prior coronary artery bypass graft surgery, as anticipated given the higher risk for restenosis and target lesion failure in these patient groups. They were also more likely to have a history of prior MI, peripheral artery disease, and coronary artery bypass graft surgery. These findings are in accordance with recent data on ISR in all comers (12), indicating a more aggressive atherosclerotic phenotype in such patients.

INTRAVASCULAR IMAGING. Intravascular imaging has a critical role in CTO PCI, as it can facilitate CTO crossing and ensure optimal stent deployment that reduces the risk for subsequent clinical events (16–19). The use of intravascular imaging in our

FIGURE 2 **Continued**

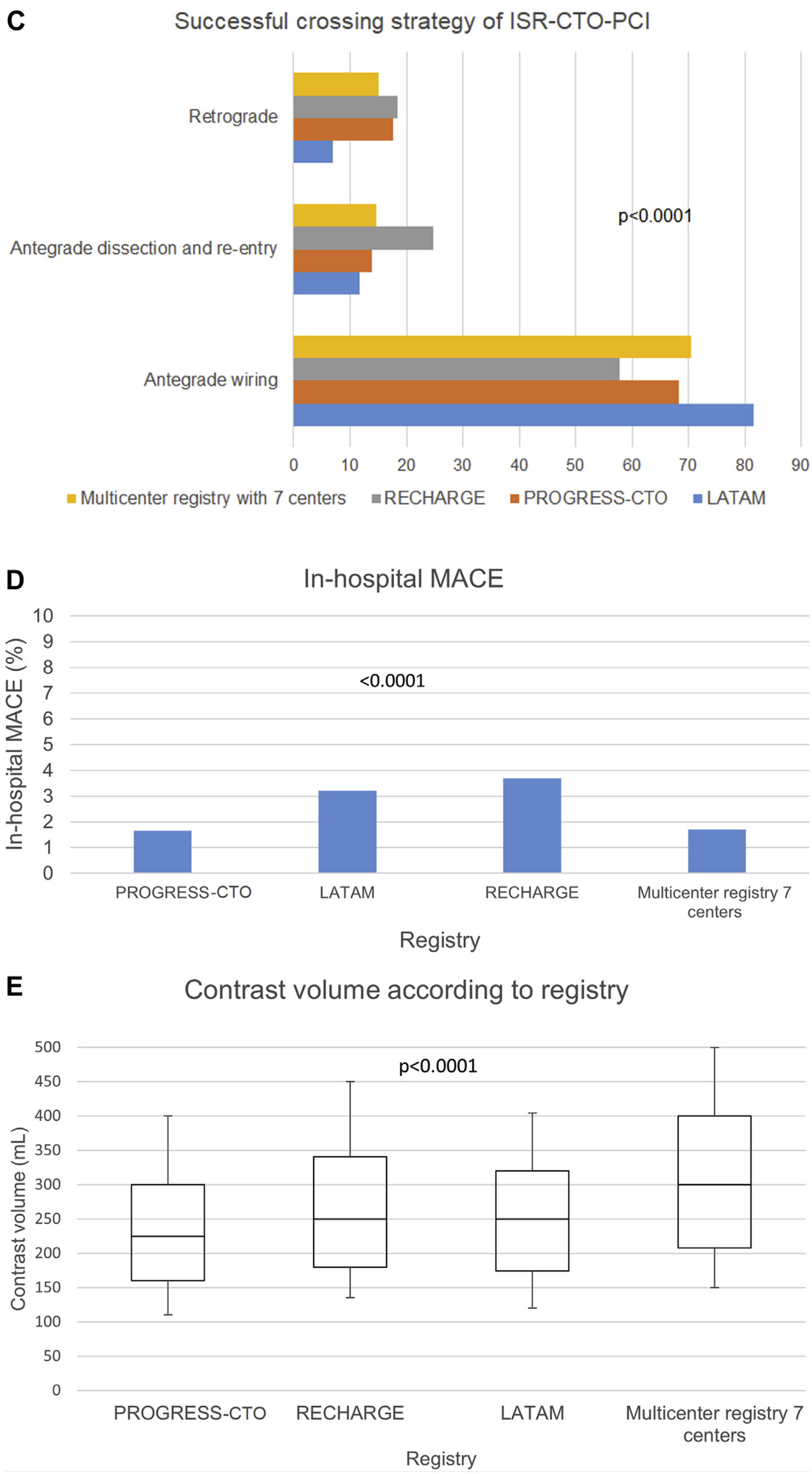
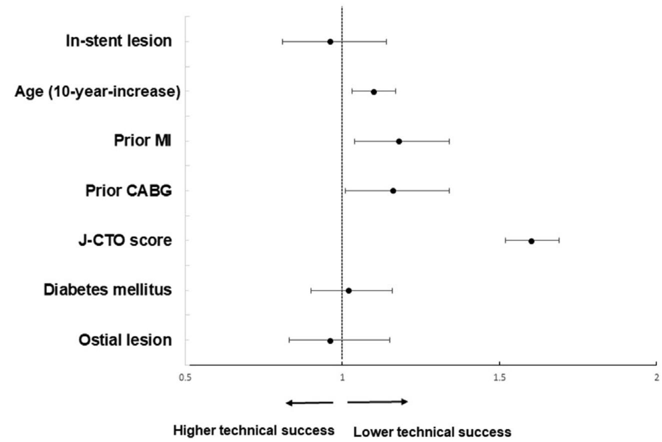


FIGURE 3 **Multivariable Logistic Regression for Technical Success**

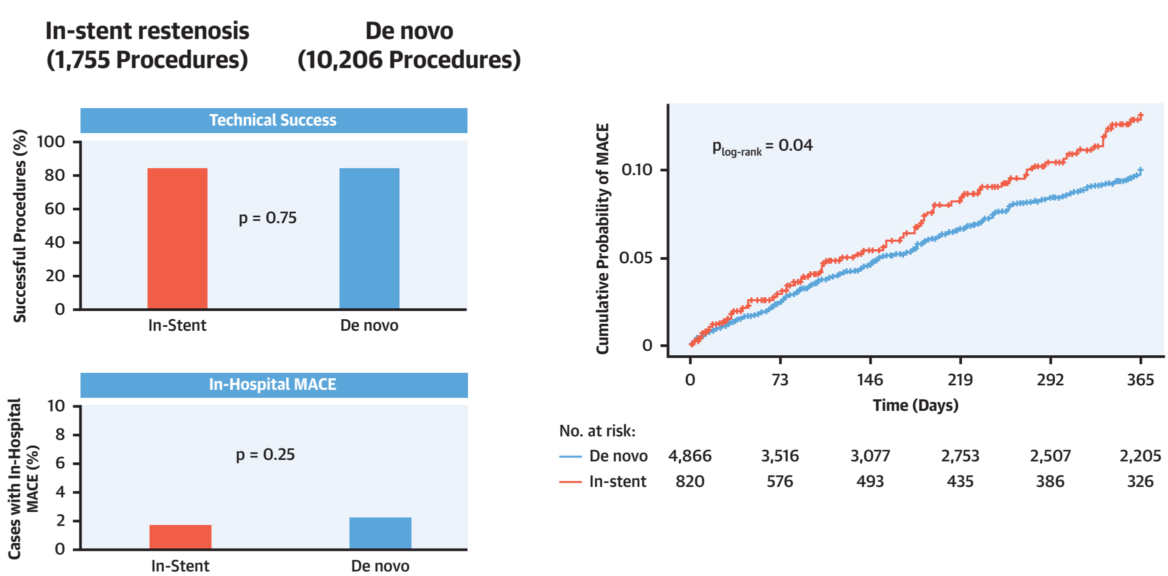


	OR	95% CI	p-value
In-stent lesion	0.96	(0.81-1.14)	0.68
Age (10-year-increase)	1.1	(1.03-1.17)	0.003
Prior MI	1.18	(1.04-1.34)	0.008
Prior CABG	1.16	(1.01-1.34)	0.037
J-CTO score	1.6	(1.52-1.69)	<0.001
Diabetes mellitus	1.02	(0.9-1.16)	0.74
Ostial lesion	0.96	(0.83-1.15)	0.89

Estimates for age and J-CTO (Multicenter CTO Registry in Japan) score are provided by 10-year or 1-point change, respectively. CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

study was higher in the in-stent group (41% vs. 33%; $p < 0.0001$), likely because of higher anticipated risk for repeat target vessel failure. Intravascular ultrasound or optical coherence tomography use is especially important for ISR PCI, as it can elucidate the mechanism of prior stent failure, facilitate adequate stent choice, and optimize the final result (20).

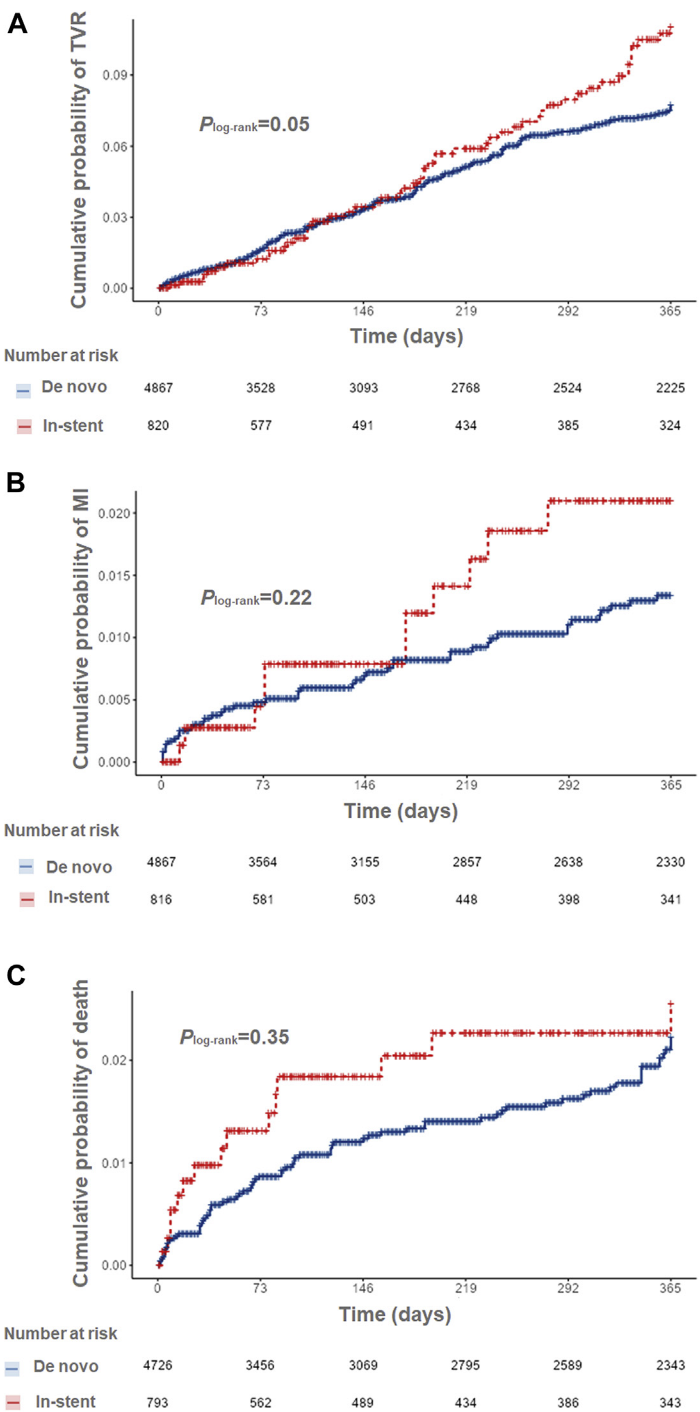
CENTRAL ILLUSTRATION **In-Stent Restenosis Chronic Total Occlusion Percutaneous Coronary Intervention: A Patient-Level Analysis of 4 Registries**



Vemmou, E. et al. J Am Coll Cardiol Intv. 2021;14(12):1308–19.

Technical success, in-hospital major adverse cardiovascular events (MACE), and 1-year MACE for in-stent versus de novo chronic total occlusion percutaneous coronary interventions.

FIGURE 4 Kaplan-Meier Estimates for TVR, MI, and Death at 1 Year



(A) Kaplan-Meier estimates for target vessel revascularization (TVR) at 1 year. **(B)** Kaplan-Meier estimates for myocardial infarction (MI) at 1 year. **(C)** Kaplan-Meier estimates for all-cause death at 1 year.

ISR CTO was not independently associated with technical success, whereas age, prior MI, prior coronary artery bypass graft surgery, and J-CTO score were, as found in several prior studies (21–25), enhancing the external validity of our findings.

TEMPORAL TRENDS. The number of in-stent CTO PCIs increased over time, likely because of improvements in CTO PCI techniques and encouraging findings from recent studies (3–7). The technical success rates of in-stent CTO PCI varied during the study period but were high overall. During 2010 and 2011, technical success for ISR CTO PCI was 100%, and the incidence of in-hospital MACE was low, but the number of attempted in-stent cases was small (10 cases in 2010 and 12 cases in 2011), and the J-CTO scores of these lesions were low.

SUBSEQUENT EVENTS. As anticipated, patients who underwent PCI of in-stent CTOs had a higher incidence of MACE during follow-up, driven by a higher incidence of target vessel revascularization. Identifying and implementing strategies to improve long-term patency after occlusive ISR is therefore critical for this group of patients. Stent optimization using intravascular imaging may help reduce the risk for recurrent failure, whereas it is unclear whether routine angiographic follow-up has a favorable risk/benefit ratio.

STUDY LIMITATIONS. First, this was an observational, retrospective study with all inherent limitations. Second, follow-up was available for only a portion of the patient population. Third, there was no clinical event adjudication by a clinical event committee. Fourth, all procedures were performed at high-volume centers by experienced operators, limiting the generalizability of the results to other institutions with limited CTO PCI experience. Fifth, there was no information on intravascular ultrasound or optical coherence tomographic findings that could aid in understanding stent failure mechanisms in individual patients.

Finally, relevant data on the type of the occluded stent in the ISR CTO group, alternative treatments to stenting (e.g., drug-coated balloons, brachytherapy), and baseline medical therapy were not available.

CONCLUSIONS

In-stent CTOs represented 15% of total cases in an analysis of 4 contemporary CTO PCI registries. Technical and procedural success rates were similar with de novo CTOs, as was the incidence of in-hospital MACE. However, at 1-year follow-up, in-stent lesions were associated with higher incidence of MACE compared with de novo lesions, driven by higher incidence of target vessel revascularizations.

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PERSPECTIVES

WHAT IS KNOWN? PCI of ISR CTO has been associated with lower success rates in some studies.

WHAT IS NEW? ISR represented 15% of total cases in an analysis of 4 multicenter CTO PCI registries. Technical and procedural success rates were similar with de novo lesions, as well as in-hospital MACE rates. However, at 1-year follow-up, in-stent lesions were associated with a higher incidence of MACE and target vessel revascularization.

WHAT IS NEXT? Additional treatment options should be developed for patients with in-stent CTOs to improve long-term patency.

REFERENCES

1. Abbas AE, Brewington SD, Dixon SR, Boura J, Grines CL, O'Neill WW. Success, safety, and mechanisms of failure of percutaneous coronary intervention for occlusive non-drug-eluting in-stent restenosis versus native artery total occlusion. Am J Cardiol 2005;95:1462–6.

2. Christopoulos G, Karmpaliotis D, Alaswad K, et al. The efficacy of "hybrid" percutaneous coronary intervention in chronic total occlusions caused by in-stent restenosis: insights from a US multicenter registry. Catheter Cardiovasc Interv 2014;84:646–51.

3. Vemmou E, Alaswad K, Karmpaliotis D, et al. Outcomes of percutaneous coronary intervention for in-stent chronic total occlusions: insights from the PROGRESS-CTO registry. J Am Coll Cardiol Intv 2020;13:1969–71.

4. Azzalini L, Dautov R, Ojeda S, et al. Procedural and long-term outcomes of percutaneous coronary intervention for in-stent chronic total occlusion. J Am Coll Cardiol Intv 2017;10:892–902.

5. de la Torre Hernandez JM, Rumoroso JR, Subinas A, et al. Percutaneous intervention in chronic total coronary occlusions caused by in-stent restenosis: procedural results and long-term clinical outcomes in the TORO (Spanish Registry of Chronic Total Occlusion Secondary to an Occlusive In-Stent Restenosis) multicentre registry. EuroIntervention 2017;13:e219–26.

6. Yoon YH, Lee PH, Lee SW, et al. Clinical outcomes after percutaneous coronary intervention for in-stent chronic total occlusion. EuroIntervention 2020;16:e472–9.

7. Lamelas P, Padilla L, Abud M, et al. In-stent chronic total occlusion angioplasty in the LATAM-CTO registry. Catheter Cardiovasc Interv 2021;97:E34–9.

8. Brilakis E. Chapter 9—complex lesion subsets. In: Brilakis E, editor. Manual of Chronic Total Occlusion Interventions. 2nd ed. San Diego, California: Academic Press, 2018:289–339.

9. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

10. Morino Y, Abe M, Morimoto T, 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. J Am Coll Cardiol Intv 2011;4:213–21.

11. Christopoulos G, Kandzari DE, Yeh RW, 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. J Am Coll Cardiol Intv 2016;9:1–9.

12. Moussa ID, Mohananey D, Saucedo J, et al. Trends and outcomes of restenosis after coronary stent implantation in the United States. J Am Coll Cardiol 2020;76:1521–31.

13. Abdel-Karim AR, Lombardi WB, Banerjee S, Brilakis ES. Contemporary outcomes of percutaneous intervention in chronic total coronary occlusions due to in-stent restenosis. Cardiovasc Revasc Med 2011;12:170–6.

14. Werner GS, Moehlis H, Tischer K. Management of total restenotic occlusions. EuroIntervention 2009;5 suppl D:D79–83.

15. Lee SH, Cho JY, Kim JS, et al. A comparison of procedural success rate and long-term clinical outcomes between in-stent restenosis chronic total occlusion and de novo chronic total occlusion using multicenter registry data. Clin Res Cardiol 2020;109:628–37.

16. Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention. Circulation 2019;140:420–33.

17. Mentias A, Sarrazin MV, Saad M, et al. Long-term outcomes of coronary stenting with and without use of intravascular ultrasound. J Am Coll Cardiol Intv 2020;13:1880–90.

18. Kim BK, Shin DH, Hong MK, et al. Clinical impact of intravascular ultrasound-guided chronic total occlusion intervention with zotarolimus-eluting versus biolimus-eluting stent implantation: randomized study. Circ Cardiovasc Interv 2015;8:e002592.

19. Shlofmitz E, Torguson R, Zhang C, et al. Impact of Intravascular Ultrasound on Outcomes Following Percutaneous Coronary Intervention in Complex Lesions (iOPEN Complex). Am Heart J 2020;221:74–83.

20. Galassi AR, Sumitsuji S, Boukhris M, et al. Utility of intravascular ultrasound in percutaneous revascularization of chronic total occlusions: an overview. J Am Coll Cardiol Intv 2016;9:1979–91.

21. Karatasakis A, Iwnetu R, Danek BA, et al. The impact of age and sex on in-hospital outcomes of chronic total occlusion percutaneous coronary intervention. J Invasive Cardiol 2017;29:116–22.

22. Tajti P, Karmpaliotis D, Alaswad K, et al. In-hospital outcomes of chronic total occlusion percutaneous coronary interventions in patients with prior coronary artery bypass graft surgery. Circ Cardiovasc Interv 2019;12:e007338.

23. Azzalini L, Ojeda S, Karatasakis A, et al. Long-term outcomes of percutaneous coronary intervention for chronic total occlusion in patients who have undergone coronary artery bypass grafting vs those who have not. Can J Cardiol 2018;34:310–8.

24. Tajti P, Karmpaliotis D, Alaswad K, et al. The hybrid approach to chronic total occlusion percutaneous coronary intervention: update from the PROGRESS CTO registry. J Am Coll Cardiol Intv 2018;11:1325–35.

25. Wang N, Fulcher J, Abeysuriya N, Adams M, Lal S. Predictors of successful chronic total occlusion percutaneous coronary interventions: a systematic review and meta-analysis. Heart 2018;104:517–24.

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