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Retrograde Recanalization of Chronic Total Occlusions in Europe

Procedural, In-Hospital, and Long-Term Outcomes From the Multicenter ERCTO Registry

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ABSTRACT

BACKGROUND A retrograde approach improves the success rate of percutaneous coronary interventions (PCIs) for chronic total occlusions (CTOs).

OBJECTIVES The authors describe the European experience with and outcomes of retrograde PCI revascularization for coronary CTOs.

METHODS Follow-up data were collected from 1,395 patients with 1,582 CTO lesions enrolled between January 2008 and December 2012 for retrograde CTO PCI at 44 European centers. Major adverse cardiac and cerebrovascular events were defined as the composite of cardiac death, myocardial infarction, stroke, and further revascularization.

RESULTS The mean patient age was 62.0 ± 10.4 years; 88.5% were men. Procedural and clinical success rates were 75.3% and 71.2%, respectively. The mean clinical follow-up duration was 24.7 ± 15.0 months. Compared with patients with failed retrograde PCI, successfully revascularized patients showed lower rates of cardiac death (0.6% vs. 4.3%, respectively; $p < 0.001$), myocardial infarction (2.3% vs. 5.4%, respectively; $p = 0.001$), further revascularization (8.6% vs. 23.6%, respectively; $p < 0.001$), and major adverse cardiac and cerebrovascular events (8.7% vs. 23.9%, respectively; $p < 0.001$). Female sex (hazard ratio [HR]: 2.06; 95% confidence interval [CI]: 1.33 to 3.18; $p = 0.001$), prior PCI (HR: 1.73; 95% CI: 1.16 to 2.60; $p = 0.011$), low left ventricular ejection fraction (HR: 2.43; 95% CI: 1.22 to 4.83; $p = 0.011$), J-CTO (Multicenter CTO Registry in Japan) score ≥3 (HR: 2.08; 95% CI: 1.32 to 3.27; $p = 0.002$), and procedural failure (HR: 2.48; 95% CI: 1.72 to 3.57; $p < 0.001$) were independent predictors of major adverse cardiac and cerebrovascular events at long-term follow-up.

CONCLUSIONS The number of retrograde procedures in Europe has increased, with high percents of success, low rates of major complications, and good long-term outcomes. (J Am Coll Cardiol 2015;65:2388–400) © 2015 by the American College of Cardiology Foundation.

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Since the first report in 1990 (1), coronary chronic total occlusion (CTO) recanalization through retrograde collateral vessels remains a technical challenge in interventional cardiology, greatly improving success rates in complex CTO lesions not amenable to antegrade techniques. Over the past 5 years, different retrograde techniques have been introduced, as well as new guidewires, microcatheters, and balloons dedicated to this approach (2-6). Japan, Europe, and the United States have published initial results (7-12), followed by larger patients cohorts (13-16).

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The aim of the present study was to describe practice, procedural outcome, in-hospital events, and long-term clinical follow-up after retrograde CTO percutaneous coronary intervention (PCI) performed by a large group of dedicated interventionalists who are members of the Euro CTO Club.

METHODS

STUDY POPULATION. The European Registry of CTOs (ERCTO) is a prospective real-world registry that includes patients treated via the retrograde or anterograde approach for 1 or more CTO lesions involving major genuine coronary arteries (>2.5 mm) or saphenous bypass conduits. Data collection was carried out at 44 centers across Europe. All patients undergoing retrograde or antegrade CTO PCI at these centers between January 2008 and December 2012 were registered prospectively. There were no exclusion criteria. Retrograde CTO PCIs were included as first-attempt procedures or as procedures after prior failed antegrade attempts in the same or other sessions. The treatment indication was symptomatic myocardial ischemia and/or evidence of reversible myocardial ischemia by perfusion imaging or stress testing. Patient follow-up was performed either by a clinical visit or by a telephone interview. At follow-up, details regarding major adverse cardiac and cerebrovascular event (MACCE) occurrence, rehospitalization for cardiovascular reasons, and symptoms were collected by physicians through the revision of clinical source documentation. The study was performed in accordance with the Declaration of Helsinki.

DEFINITIONS AND STUDY OUTCOMES. Coronary CTOs were defined as angiographic evidence of total occlusions with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 and estimated durations of at least 3 months. Occlusion duration was divided into 3 levels of certainty, as suggested by the EuroCTO Club consensus document (17). Patients were considered to have undergone retrograde CTO PCI if a guidewire was introduced into a collateral channel that supplied the target vessel distal to the lesion (9). A procedure was defined as an antegrade CTO PCI if no guidewire was introduced into a collateral channel, as previously defined. Procedural success was defined as angiographic success (final residual stenosis <20% by visual estimation and TIMI flow grade 3 after CTO recanalization). Clinical success was defined as a procedural success without periprocedural complications. In-hospital MACCEs were defined as the composite of non-Q-wave and Q-wave myocardial infarction (MI), recurrent angina requiring urgent repeat revascularization with PCI or coronary bypass surgery, stroke, and death. Non-Q-wave MI was defined as creatine kinase-MB enzyme elevation >3 times the upper limit of normal. When new pathological Q waves, in addition to enzyme elevation, were observed on the electrocardiogram, the event was defined as a Q-wave MI. In all patients, creatine kinase and creatine kinase-MB were evaluated 6 h after the procedure and until their normalization if levels were abnormal (18,19). The complexity of CTO lesion was assessed through J-CTO (Multicenter CTO Registry in Japan) score (0 = easy,

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CART = controlled antegrade retrograde tracking

CI = confidence interval

CTO = chronic total occlusion

HR = hazard ratio

MACCE = major adverse cardiac and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

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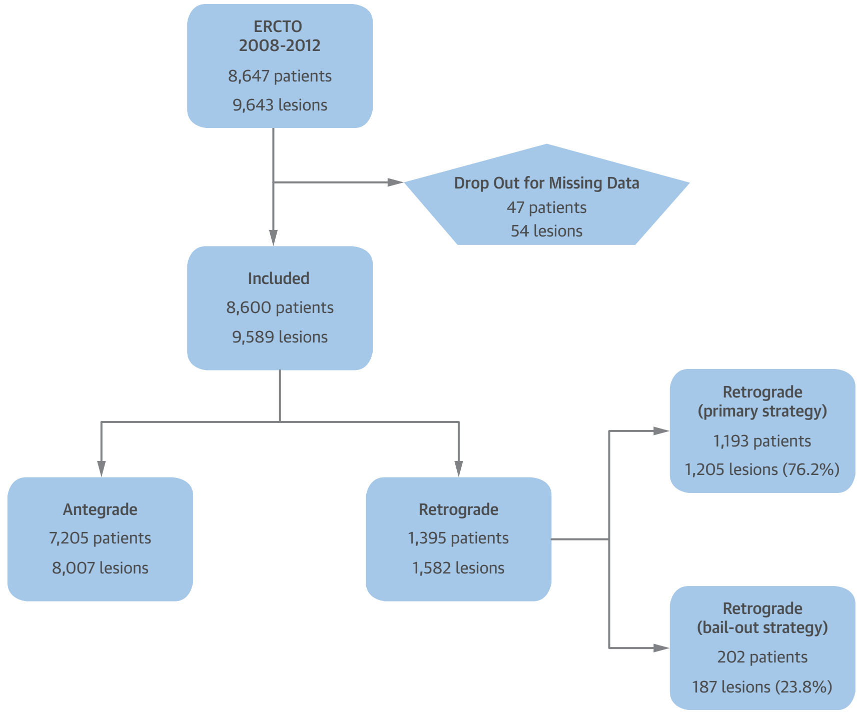
FIGURE 1 Flowchart of the Study Population



Patients included in the multicenter European Registry of CTOs (ERCTO) Registry from 2008 to 2012.

1 = intermediate, 2 = difficult, ≥3 = very difficult) (20). At follow-up, MACCEs were defined as the composite of cardiac death, MI, stroke, and further need for revascularization. Dyspnea and angina were assessed according to New York Heart Association and Canadian Cardiovascular Society classifications, respectively, before the indexed procedure and during follow-up.

INTERVENTIONAL PROCEDURES. All patients received optimal intravenous hydration the days before and after PCI. Patients received an initial bolus of intravenous unfractioned heparin (100 IU/kg). The activated clotting time was monitored every 30 min to determine if an additional bolus of unfractioned heparin was necessary to maintain an activated clotting time >250 s. Upstream use of glycoprotein IIb/IIIa inhibitor therapy or bivalirudin was avoided.

Choice of CTO revascularization strategy was left to the operator's discretion. All procedures were performed via the femoral route, with double coronary cannulation and contralateral selective injection. Seven-French guiding catheters were used in most cases. Several guidewire strategies were used, including the single-wire technique, the parallel-wires technique, the intravascular ultrasound-guided wiring technique, and retrograde wiring through collateral vessels, such as simple retrograde wiring, kissing wires, the knuckle technique, and the controlled antegrade retrograde tracking (CART) and reverse CART techniques, as previously described (9,17). Only drug-eluting stents were implanted.

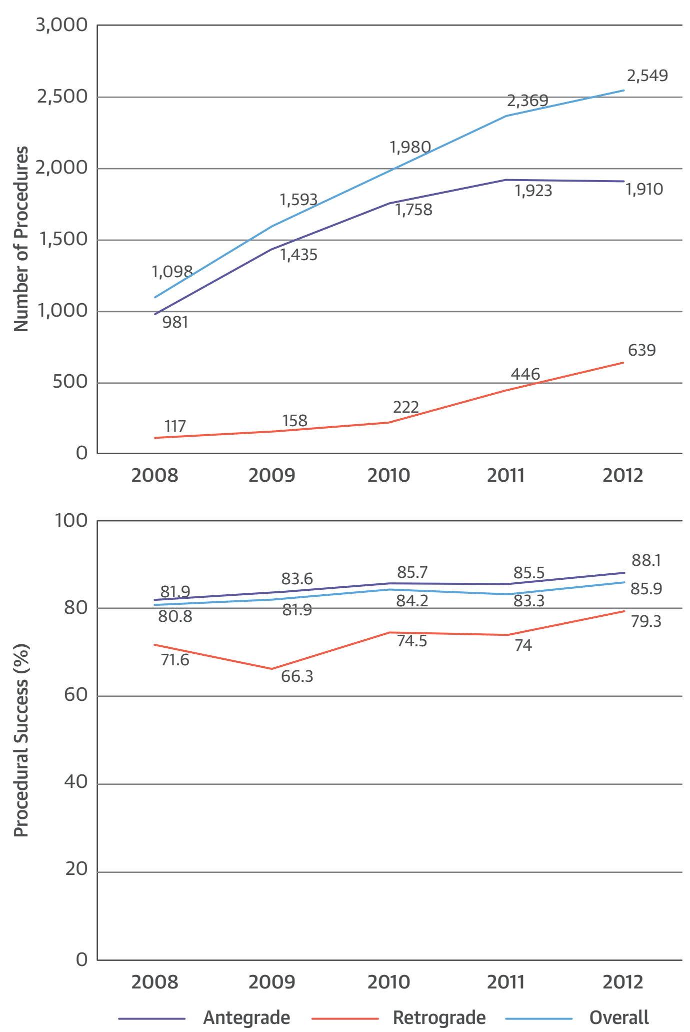
STATISTICAL ANALYSIS. Clinical characteristics, angiographic features, and in-hospital and follow-up events were reported through standard descriptive analyses for large samples assumed to follow a normal distribution. Continuous variables are presented as mean ± SD and categorical variables as frequencies and percents. The Cochran-Armitage trend test was used to compare success rates between years. Student *t* tests and chi-square tests (or Fisher exact tests when at least 25% of values showed expected cell frequencies <5) were used for comparison regarding procedural success, except for J-CTO score, for which the Wilcoxon test was used. We tried to identify clinical and/or angiographic prognostic factors of procedural failure through logistic regression analysis among age, sex, diabetes, ejection fraction <35%, history of MI, prior coronary artery bypass grafting (CABG), prior PCI, occlusion duration (<12 or ≥12 months [the median of the likely and certain] or undetermined), occlusion length (<20 or ≥20 mm), interventionalist experience (<50, 50 to 100, or >100 retrograde CTO PCIs), and J-CTO score. Univariate analyses were performed, and multivariate Cox proportional hazards regression modeling using purposeful selected covariates was applied to determine the independent predictors of long-term MACCE occurrence. All univariate variables with p values <0.10 were included in the model. Variables judged to be of clinical importance from previous published research were included in the multivariate model-building process despite p values >0.10. The univariate model included the following clinical and angiographic variables: age, sex, diabetes, chronic obstructive pulmonary disease, ejection fraction <35%, prior MI, prior CABG, prior PCI, CTO vessel, occlusion duration, number of previous attempts, CTO length, J-CTO score ≥3, number of implanted stents, and stent length. Regarding symptom changes, McNemar's test was used to compare angina and dyspnea status before the index procedure and during follow-up. Two-tailed p values <0.05 were considered to indicate statistically significant differences for all analyses performed. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CLINICAL AND LESION CHARACTERISTICS. During the 5-year study period at the 44 centers of the EuroCTO Club, retrograde CTO PCI was performed in 1,395 patients, corresponding to 1,582 lesions. Antegrade CTO PCI was performed in 7,205 patients, corresponding to 8,007 lesions (Figure 1). Overall, 16 centers (36.4%) contributed to the 5-year retrograde experience; 5 (11.4%) started retrograde CTO interventions only in the last year of the study (2012), while the contribution of the remaining 23 centers (52.2%) in retrograde CTO PCI ranged from 2 to 4 years of experience.

The relative number of retrograde procedures increased over time, reaching 25.1% of all CTOs treated in 2012 (Figure 2). Retrograde CTO procedure volumes of ≤50, >50 but <100, and >100 were attained by 35, 5, and 4 centers, respectively, during the study period, corresponding to 530, 303, and 562 patients enrolled. Baseline patient clinical characteristics of the retrograde CTO cohort are shown in Table 1 and baseline lesion characteristics in Table 2 according to procedural success or failure. The mean age was 62.0 ± 10.4 years, and 88.5% were men. The CTO target vessel was the right coronary artery (70.4%), circumflex coronary artery (7.8%), left anterior descending coronary artery (20.3%), and left main artery or a bypass graft (1.5%). Prior failed antegrade attempts (by non-CTO-dedicated operator) were documented in 42.5% of patients, and these did not affect the procedural success rate (p = 0.97). At the time of enrollment in ERCTO, the retrograde approach was used as a first strategy in 76.2% of cases and after prior failed antegrade

FIGURE 2 Numbers of Procedures and Rate of Procedural Success



Antegrade, retrograde, and total percutaneous coronary intervention procedure volumes from 2008 to 2012 **(A)** and corresponding procedural success rates per year **(B)**, which have significantly increased over the years.

TABLE 1 PCI Patient and Clinical Characteristics According to Procedural Success, 2008 to 2012

	Overall (n = 1,395)	Procedural Success (n = 1,060 [76%])	Procedural failure (n = 335 [24%])	p Value
Age, yrs	62.0 ± 10.4	61.4 ± 10.5	63.9 ± 10.0	0.0001
Men	88.5	86.6	89.4	0.15
Current or former smokers	57.9	58.9	54.7	0.13
Clinical presentation				
Asymptomatic	10.0	10.4	9.6	
Stable angina	84.1	84	84.4	0.95
Unstable angina	5.7	5.5	6.0	
MI	0.2	0.3	0.0	
Hypertension	77.3	77.5	76.7	0.74
Hyperlipidemia	78.9	79.5	76.7	0.27
Diabetes	29.0	27.5	33.7	0.04
LVEF <35%	6.0	6.2	5.4	0.62
History of MI	43.5	44.2	41.5	0.33
History of CABG	17.6	16.9	20.0	0.14
History of stroke	2.5	1.9	4.5	0.007
Prior PCI	55.9	55.8	56.1	0.96
Coronary disease status				0.32
1-vessel disease	40.2	39.9	41.3	
2-vessel disease	31.7	32.7	28.7	
3-vessel disease	28.1	27.4	30.0	

Values are mean ± SD or %.

CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Lesion Characteristics According to Procedural Success, 2008 to 2012

	Overall (n = 1,582)	Technical Success (n = 1,191 [75%])	Technical Failure (n = 391 [25%])	p Value
CTO target vessel				0.20
RCA	70.4	69.4	73.4	
LCX	7.8	3.9	6.1	
LAD	20.3	20.9	18.4	
LM/graft	1.5	1.3	2.0	
Prior failed antegrade attempt for CTO PCI	42.5	42.6	42.5	0.97
CTO duration determined (months) (n = 1,011 [63.9%])	46.3 ± 63.8	44.2 ± 62.1	52.9 ± 68.9	0.08
J-CTO score for retrograde	3 (2-3)	3 (2-3)	3 (2-3)	0.002
Occlusion length, mm	38.4 ± 22.5	36.3 ± 21.6	38.4 ± 25.0	0.01
Stump morphology				0.0005
Tapered	27.6	29.5	21.7	
Blunt	55.8	55.7	56.4	
Cannot be identified	16.6	14.8	21.9	
Proximal tortuosity				0.0004
Straight	42.5	44.1	37.6	
Slight	14.7	15.0	13.6	
Moderate	28.5	28.8	27.6	
Severe	9.7	8.1	14.6	
Not applicable	4.6	3.9	6.6	
Heavy calcification	20.2	16.6	31.0	<0.0001

Values are %, mean ± SD, or median (interquartile range).

CTO = chronic total occlusion; J-CTO = Multicenter CTO Registry in Japan; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

attempts (during the same procedure) in 23.8% of cases. J-CTO scores were statistically higher in lesions with procedural failures (p = 0.002). The presence of heavy calcification, found in 20.2% of lesions, was significantly associated with procedural failure (p < 0.0001).

PROCEDURAL CHARACTERISTICS, COMPLICATIONS, AND IN-HOSPITAL OUTCOMES. Table 3 shows procedural characteristics of the retrograde cases. The retrograde strategy as the first approach was more successful than after a failed antegrade approach (82.2% vs. 53.1%; p < 0.001). In successful cases, the retrograde crossing technique was CART (13.9%), reverse CART (16%), touching wires (22%), or simple retrograde wire crossing (31.2%). In the remaining cases (17%), the operator did not describe the retrograde technique used.

The retrograde route was through septal collateral vessels in 62.7% of cases, epicardial collateral vessels in 13.4% and bypass grafts in 3.9%. In 20.0% of cases, information was not available. In successful cases, drug-eluting stents were implanted, with a mean stent length of 74.3 ± 32.8 mm. The mean procedural time was 156.3 ± 63.5 min, mean fluoroscopy time 66.7 ± 36.3 min, and mean contrast volume 379.3 ± 185.9 ml. These values were influenced by J-CTO score for all 3 parameters (p < 0.001 for all), as shown in Figure 3.

Thirteen patients (0.8%) experienced in-hospital MACCEs in the retrograde CTO cohort, compared with 0.5% of patients in the anterograde group. Table 4 reports complications and in-hospital outcomes with retrograde procedures. No differences were observed in terms of MACCEs, Q-wave MI, non-Q-wave MIs, coronary perforation, or cardiac tamponade according to the collateral route used for the retrograde approach (p = NS for all). Compared with patients who underwent the anterograde approach, those who underwent retrograde PCI experienced higher rates of complications, particularly coronary perforations and tamponade (Online Table 1).

SUCCESS RATES. Overall, the procedural success rate was 75.3%. This rate has increased since 2009 (73.5%, 65.8%, 73.0%, 74.7%, and 79.2% annual success rates from 2008 to 2012, respectively). Clinical success was achieved in 1,126 lesions (71.2%). Procedural success for retrograde cases related to retrograde J-CTO score and operator experience is shown in Figure 4.

Both univariate and multivariate prognostic analyses (Table 5) demonstrated that low experience and lesion complexity (measured by J-CTO score) negatively affected the final outcome ($p < 0.0001$). Age (per 10-year increase) was also found to be an independent prognostic factor at multivariate analysis (odds ratio: 1.19; 95% confidence interval [CI]: 1.03 to 1.34; $p = 0.02$).

CLINICAL FOLLOW-UP. Among the study population, data on clinical follow-up were available in 931 patients (66.7%). These patients were more frequently smokers and dyslipidemic and showed a higher rate of prior PCI compared with those lost to follow-up (Online Table 2). The mean clinical follow-up period was 24.7 ± 15.0 months (median 23 months). Cardiac death occurred in 18 patients (1.9%), while all-cause mortality was 3.9%. MI and stroke occurred in 32 (3.4%) and 6 (0.6%) patients, respectively; the rate of further revascularization, either percutaneously or surgically, was 13%. Overall, MACCEs occurred in 127 patients (13.6%).

In comparison with patients with failed retrograde PCI, successfully revascularized patients showed lower rates of cardiac death (0.6% vs. 4.3%, respectively; $p < 0.001$), MI (2.3% vs. 5.4%, respectively; $p = 0.001$), further revascularization (8.6% vs. 23.6%, respectively; $p < 0.001$), overall MACCEs (8.7% vs. 23.9%, respectively; $p < 0.001$) (**Figure 5**), and rehospitalization (14.2% vs. 25%, respectively; $p < 0.001$).

The multivariate Cox regression analysis identified female gender (hazard ratio [HR]: 2.06; 95% CI: 1.33 to 3.18; $p = 0.001$), prior PCI (HR: 1.73; 95% CI: 1.16 to 2.60; $p = 0.011$), low left ventricular ejection fraction (HR: 2.43; 95% CI: 1.22 to 4.83; $p = 0.011$), J-CTO score ≥3 (HR: 2.08; 95% CI: 1.32 to 3.27; $p = 0.002$), and procedural failure (HR: 2.48; 95% CI: 1.72 to 3.57; $p < 0.001$) as independent predictors of MACCEs at long-term follow-up (**Figure 6**). Compared with angina and dyspnea status before the index retrograde PCI, patients who underwent retrograde CTO PCI showed a significant reduction in symptoms during follow-up (**Figure 7**).

TABLE 3 Procedural Characteristics According to Procedural Success, 2008 to 2012

	Overall (n = 1,582)	Procedural Success (n = 1,191 [75%])	Procedural Failure (n = 391 [25%])	p Value
Collateral used				
Septal	62.7	65.3	56.0	
Epicardial	13.4	13.8	11.4	
Bypass graft	3.9	4.3	2.4	
Missing	20.0	16.7	30.2	
Retrograde crossing technique				NA
CART	–	13.9	–	
Reverse CART	–	16.0	–	
Touching wire	–	22.0	–	
Retrograde wire crossing	–	31.2	–	
Missing	–	17.0	–	
Retrograde as first approach	76.2	83.2	55.0	<0.0001
Retrograde after antegrade failed approach	23.8	16.8	45.0	
Intravascular ultrasound use	9.2	10.6	NA	NA
Stent diameter, mm	NA	3.23 ± 0.44	NA	NA
Total stent length, mm	NA	74.3 ± 32.8	NA	NA
Number of stents	NA	2.85 ± 1.25	NA	NA
Drug-eluting stents only	NA	85.4	NA	NA
Bare-metal stents only	NA	2.4	NA	NA
Both types of stent	NA	9.7	NA	NA
Missing	NA	2.5	NA	NA
Balloon angioplasty only	NA	2.2	NA	NA
Total procedure time, min	156.3 ± 63.5	159.1 ± 62.9	147.9 ± 64.8	0.003
Total fluoroscopy time, min	66.7 ± 36.3	67.5 ± 34.9	64.3 ± 40.0	0.16
Total contrast volume, ml	379.3 ± 185.9	387.7 ± 181.4	353.6 ± 196.9	0.002

Values are % or mean ± SD.
CART = controlled antegrade retrograde tracking; NA = not applicable.

DISCUSSION

From 2008 to 2012, highly skilled CTO-dedicated operators in the ERCTO registry performed retrograde approach procedures in 16.5% of cases. The number of retrograde procedures increased in 2011 and 2012, reaching 25% in the latter year, and was associated with high procedural and clinical success (75.3% and 71.2%, respectively), low major complication rates, and good long-term outcomes.

Although favorable outcomes of the retrograde approach in CTO revascularization were recently achieved in selected centers (13–15), operators did not unanimously embrace this technique. Indeed, success depends on the operator's skill and experience. More recently, the safety and effectiveness of the retrograde PCI approach for CTO performed by independent operators in the real world were established by a scientific organization called the Retrograde Summit, which published the results of a registry conducted by Tsuchikane et al. (16). This study was conducted over 2-year period and included 801 patients with CTOs revascularized via the retrograde approach (26.6% of the CTOs treated); overall procedural and clinical success rates were 84.8% and 83.8%, respectively (16). They demonstrated that the use of channel dilator-modified strategies of the retrograde approach significantly improved the success rate, except in the case of severe calcifications at the CTO location.

The results of the present study show slightly lower procedural success (75%) than obtained by the Japanese operators (16), with a similar difference

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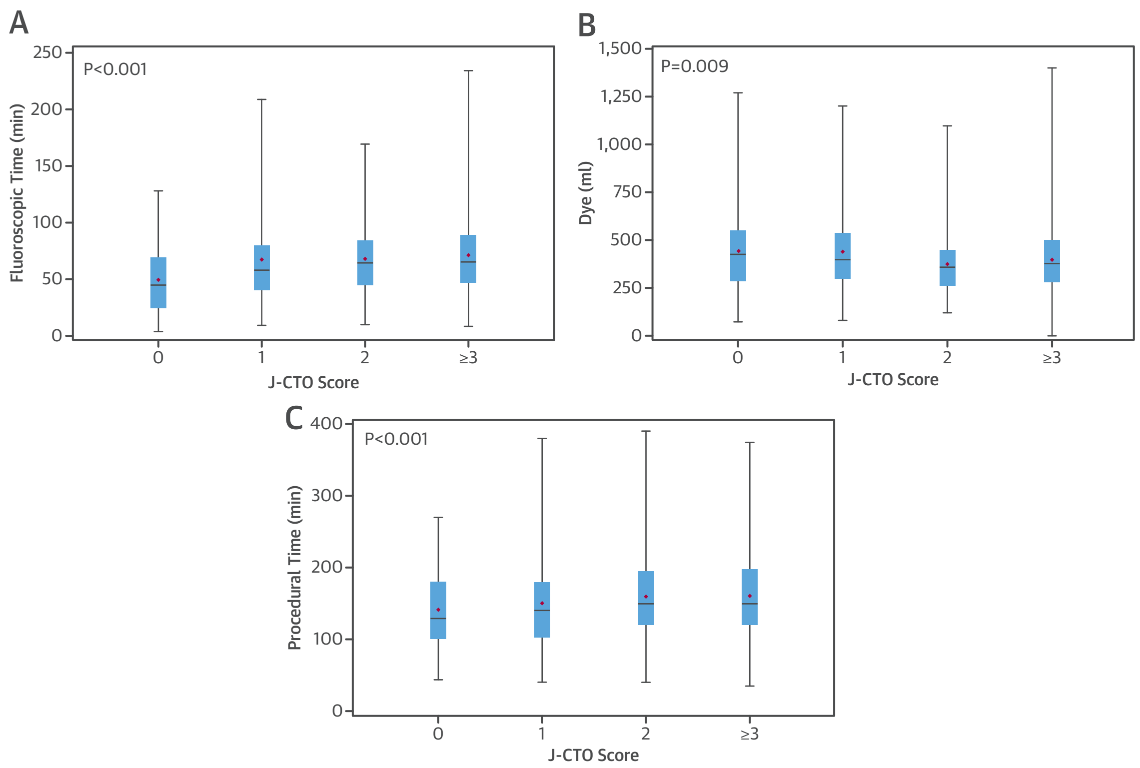
FIGURE 3 **Procedural Details According to J-CTO Score**



Boxplot (minimum, first quartile, median, mean, third quartile, and maximum) of **(A)** fluoroscopic time, **(B)** dye consumption according to J-CTO (Multicenter CTO Registry in Japan) score, and **(C)** procedural time.

TABLE 4 **Procedural Complications and In-Hospital Outcomes in Retrograde Lesions, 2008 to 2012**

	Overall (n = 1,582)	Procedural Success (n = 1,191)	Procedural Failure (n = 391)	p Value, Success vs. Failure
Procedural complications	108 (6.8)	65 (5.5)	43 (11.0)	0.0001
PE without tamponade	9 (0.6)	7 (0.6)	2 (0.5)	0.99
PE with tamponade	15 (1.0)	10 (0.8)	5 (1.3)	0.55
PE, surgical intervention	2 (0.1)	0 (0.0)	2 (0.5)	NC
Collateral perforation/ hematoma	31 (2.0)	18 (1.5)	13 (3.3)	0.02
Stent thrombosis	3 (0.2)	2 (0.1)	1 (0.2)	NA
Vascular complications	16 (1.0)	10 (0.8)	6 (1.5)	0.24
Collateral donor vessel thrombus or dissection	30 (1.9)	17 (1.4)	13 (3.3)	0.02
In-hospital outcomes				
Non-Q-wave MI	5 (0.3)	3 (0.3)	2 (0.5)	NC
Q-wave MI	2 (0.1)	2 (0.2)	0 (0.0)	NC
Emergency CABG	2 (0.1)	1 (0.08)	1 (0.2)	NC
Emergency re-PCI	2 (0.1)	1 (0.08)	1 (0.2)	NC
Death	2 (0.1)	0 (0.0)	2 (0.5)	NC
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	NC

Values are n (%).
PE = pericardial effusion; NC = statistical data do not converge; other abbreviations as in Tables 1 and 3.

(4%) between clinical and procedural success rates. Similar results were obtained in a multicenter registry in the United States, with procedural success of 81.4% and clinical success of 79.4% (15). A possible explanation for the lower success rate in our study compared with the Japanese and American registries could be ascribed to the larger numbers of patients and operators included in the study. Furthermore, given that the retrograde technique was used also after failed antegrade attempts, its use is determinant to achieve success in those cases with unfavorable anatomy for antegrade recanalization; thus a decreased success rate with the antegrade approach is an expected finding.

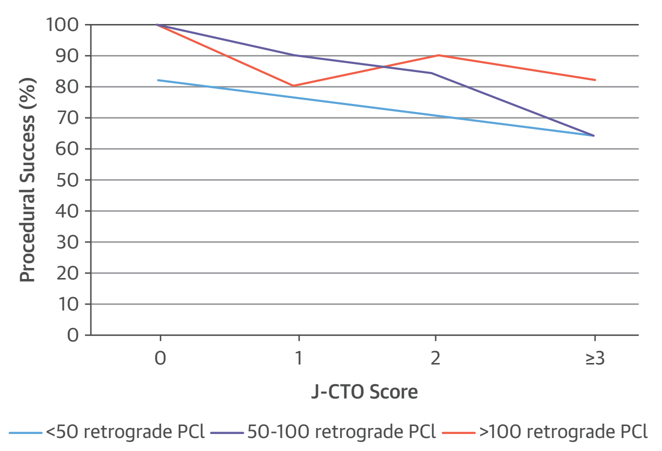
In our patients, higher success rates were observed when the retrograde approach was the primary strategy adopted, compared with its use after antegrade failure (82.2% vs. 53.1%; $p < 0.001$). This is similar to our earlier European experience for some operators (9) and highlights how in very complex CTOs with expected antegrade low success rate, the retrograde approach might be preferable as the primary strategy in experienced hands. Indeed, a first antegrade failure may lead to higher operator and patient fatigue and increased contrast consumption or radiation exposure, which might compromise the success of the retrograde bailout strategy, the latter being the only reliable alternative way of recanalization in some very complex lesions, given the recent development of dedicated devices and wires for such a strategy.

Furthermore, the retrograde approach might be a feasible procedure when antegrade wiring seems to be very difficult because of anatomic factors (ostial CTO, absence of stump, CTO length >30 mm, presence of side branch or heavy calcification at the proximal cap, and proximal vessel tortuosity), in the presence of visible and continuous collateral vessels, healthy donor vessels, and in repeat attempt procedures after previous failures (21,22).

Among the different techniques used, the CART and reverse CART techniques were used in almost 30% of cases, as well as retrograde wire crossing (30%). The kissing wire technique was used in 22% of cases. In the remaining 17% of cases, data were missing. We had no strict rules for the selection of a particular technique, and sometimes a combination of techniques was necessary to achieve success. However, reverse CART has recently become the technique of choice by the use of a channel dilator, as pointed out in other reports (12,16). In contrast, placing an antegrade wire may be wise and in many cases helpful to target the proximal CTO cap.

In this study, we found that procedural success decreased with patient age, presence of diabetes, and history of previous stroke, probably because of underlying severe and diffuse atherosclerosis in these patients. Furthermore, age (per 10-year increase) was an independent predictor of procedural failure by multivariate analysis. In these older patients, operators might be more reluctant to perform more cumbersome procedures. In a different setting (acute coronary syndrome), Jolly et al. (23) demonstrated that procedural volume and expertise are important for PCI success and outcome, particularly for the radial approach. Thompson et al. (14) showed that in the United States, CTO experience measured by CTO-coronary PCI volume is associated with improved technical success rates, without compromising patient safety. Similarly, in this study, we showed that operators' experience was highly related to procedural success in the setting of retrograde procedures. Importantly, procedural success was associated with better outcomes.

FIGURE 4 Procedural Success According to J-CTO Score and Operator Experience



Procedural success according to J-CTO (Multicenter CTO Registry in Japan) score and operator experience in retrograde procedures: <50 percutaneous coronary interventions (PCIs) **(blue)**, 50 to 100 PCIs **(purple)**, and >100 PCIs **(salmon)**.

THE J-CTO SCORE AS A DIFFICULTY-GRADING AND ASSESSMENT TOOL. The prediction rule based on the J-CTO score was recently found to be closely associated with successful antegrade recanalization (20). We proposed the J-CTO score as an objective tool for predicting the difficulty level also for the retrograde approach and found that this score was useful for assigning procedural success in relation to

TABLE 5 Univariate and Multivariate Logistic Regression Modeling, Procedural Failure

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age, per 10-yr increase	1.24	1.11–1.39	0.0002	1.19	1.03–1.34	0.02
Men	0.72	0.51–1.02	0.07	0.70	0.47–1.05	0.08
Diabetes	1.24	0.97–1.59	0.09	1.16	0.86–1.55	0.34
Ejection fraction <35%	0.85	0.52–1.40	0.52	0.89	0.50–1.58	0.68
History of MI	0.84	0.67–1.07	0.15	0.91	0.68–1.20	0.48
History of CABG	1.21	0.91–1.63	0.19	1.22	0.81–1.64	0.44
Prior PCI	1.01	0.80–1.27	0.93	0.98	0.75–1.32	0.95
Occlusion duration						
≥12 vs. <12 months	1.33	0.98–1.79	0.07	1.33	0.93–1.89	0.10
Undetermined vs. <12 months	1.44	1.04–2.00		1.51	1.03–2.20	
Occlusion length ≥20 vs. <20 mm	1.23	0.85–1.78	0.27	0.96	0.59–1.56	0.86
Experience			<0.0001			<0.0001
<50 vs. >100 procedures	2.47	1.88–3.26		3.00	2.14–4.21	
50–100 vs. >100 procedures	2.36	1.72–3.23		2.04	1.42–2.92	
J-CTO score			0.01			0.004
Easy vs. very difficult	0.47	0.16–1.38		0.56	0.10–2.91	
Intermediate vs. very difficult	0.74	0.48–1.14		0.56	0.33–0.95	
Difficult vs. very difficult	0.64	0.47–0.87		0.55	0.38–0.79	

CI = confidence interval; J-CTO = Multicenter CTO Registry in Japan; OR = odds ratio; other abbreviations as in Table 1.

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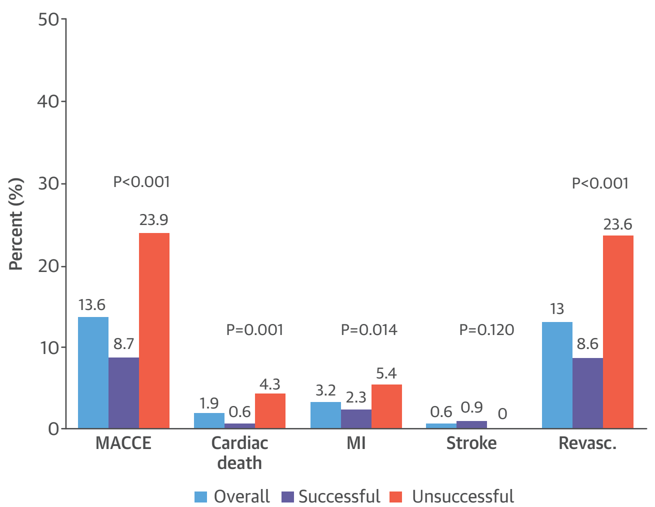
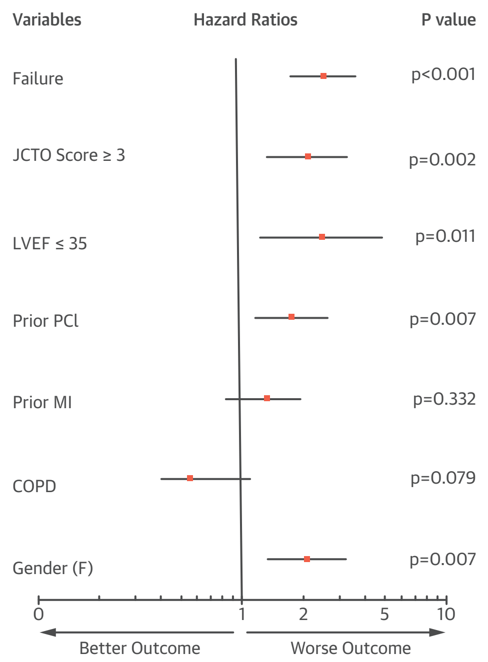
FIGURE 5 Clinical Outcome According to Procedural Success



Patients with successful retrograde percutaneous coronary intervention (PCI) showed lower rates of overall major adverse cardiac and cerebrovascular events (MACCEs), cardiac death, myocardial infarction (MI), and need for further revascularization (Revasc), compared with those in whom retrograde PCI failed.

FIGURE 6 Predictors of Long-Term Clinical Outcomes



Female (F) sex, prior percutaneous coronary intervention (PCI), impaired left ventricular ejection fraction (LVEF), J-CTO (Multicenter CTO Registry in Japan) score ≥3, and procedural failure were independent predictors of major adverse cardiac and cerebrovascular events at long-term follow-up. COPD = chronic obstructive pulmonary disease.

operators' levels of skill for the objectively determined difficulty of dealing with these lesions. Indeed, procedural success in minimally and moderately experienced retrograde operators decreased with increased J-CTO score, in contrast to experienced operators. Furthermore, age (per 10-year increase) and increased J-CTO score were significantly associated with increased procedural failure, confirming that prediction of success should take into account these latter predictors. Interestingly, even longer procedural and fluoroscopy times were significantly related to increased J-CTO score, apart from contrast load.

OUTCOME AFTER RETROGRADE RECANALIZATION. There are several studies suggesting that successful CTO PCIs are associated with better outcomes than failed CTO revascularization procedures (24–27). Niccoli et al. (28) showed in a cohort of 317 consecutive patients that successful CTO revascularization can reduce the rate of 3-year cardiac events in comparison with unsuccessful procedures (9% vs. 26%, respectively; $p = 0.008$); moreover, the investigators reported a worse prognosis in patients affected with multivessel disease.

Recently, Jones et al. (29) reported in a single-center experience the long-term survival of patients with stable angina who underwent CTO PCI attempts, showing a reduction of mortality of patients with successful CTO revascularization, in comparison with patients with unsuccessful CTO PCI (4.5% vs. 17.2%, respectively; $p < 0.0001$). Several reasons may explain this fact, including the complications related to CTO failure, which can lead to major adverse events. Moreover, PCI failure can be a marker of disease burden and other comorbidities that might limit the vigor of CTO attempts.

A recent meta-analysis by Joyal et al. (25) addressed the outcomes of patients who underwent successful versus unsuccessful CTO interventions. Although no randomized trial was included, the investigators analyzed 13 observational studies comparing PCI with planned medical therapy. This analysis demonstrated a survival benefit for those who underwent CTO recanalization (14.3% vs. 17.5%; odds ratio: 0.56) and reductions in the need for subsequent CABG and in residual or recurrent angina.

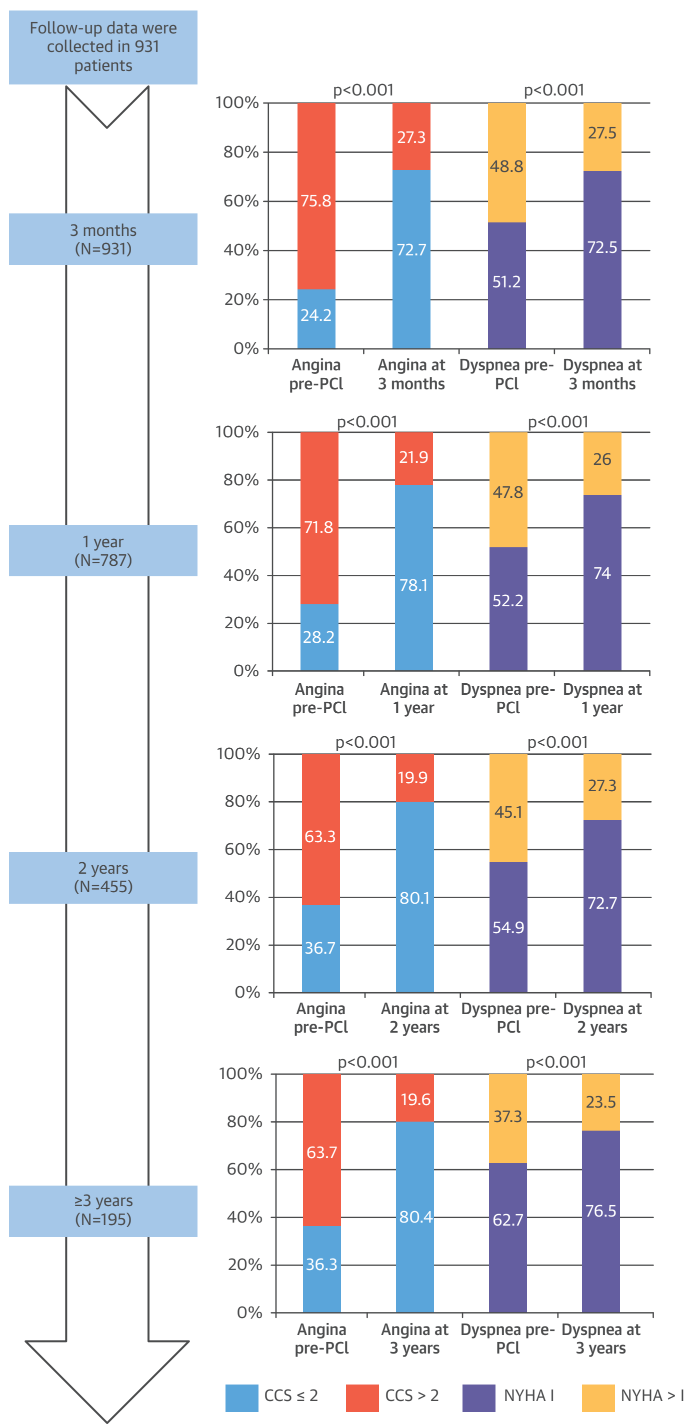
Mehran et al. (24) reported long-term outcomes in a prospective multicenter registry, showing that successful PCI was an independent predictor of lower cardiac mortality and a reduced need for CABG. Similar results were shown by a large recent analysis of the UK Central Cardiac Audit Database, in which successful CTO PCI was associated with improved long-term survival (30).

We report the short- and long-term outcomes of retrograde CTO revascularization in a large cohort of patients, showing the safety of the retrograde approach and the good prognostic impact of attaining angiographic success in the setting of a complex CTO procedure. Considering the complexity of attempted lesions, MACCE and further revascularization rates (13.6% and 13%, respectively) were satisfactory and comparable with previous outcomes by the antegrade approach (11,26,31). Very recently, Michael et al. (32) reported the only other retrograde 2-year clinical follow-up in a small group of 41 patients, showing that although the retrograde approach was safe, it was associated with a high rate of further revascularization (45%), likely due to longer stent lengths, more complex lesions, and greater use of dissection and re-entry techniques compared with antegrade procedures. The higher rates of need for further revascularization might be explained by the limited number of patients and a success rate as low as 65.8% (32). Indeed, in our cohort, this rate was higher in the unsuccessful retrograde PCI group (23.6% vs. 8.6%; $p < 0.001$).

In accordance with previous studies, we found that independent predictors of MACCEs were procedural failure (24,28,33) and female sex (34). As expected, low ventricular ejection fraction and prior PCI were also associated with MACCE, and for the first time, we showed that J-CTO score was a predictor of an unfavorable long-term outcome. This might be related to the higher atherosclerotic burden and lesion complexity of patients with higher J-CTO score, requiring longer stent segment implantation.

STUDY LIMITATIONS. As in other retrograde CTO registries, this study was limited by its observational design, in which unmeasured variables and selection bias on the part of operators toward cases may have influenced the results. Indeed, patients were treated by highly skilled, experienced operators; therefore, the results may not be generalized to less experienced operators in the real world. In addition, procedures were performed over a period when changes in operator experience and techniques occurred at different institutions. Clinical follow-up was missing in approximately one-third of the initial cohort, and the follow-up period was not homogeneous between patients (Online Figure 1). However, this registry represents the largest study reporting long-term follow-up after retrograde CTO PCI, with a median follow-up period of 23 months. To control the quality and reliability of outcome results presented, we included only centers able to provide satisfactory rates of follow-up data. Of note, patients with more comorbidities or prior PCI were

FIGURE 7 Changes in Angina and Dyspnea Status After Retrograde CTO PCI



Patients who underwent retrograde percutaneous coronary intervention (PCI) showed a reduction in symptoms (angina and dyspnea) during the follow-up period. CCS = Canadian Cardiovascular Society; CTO = chronic total occlusion; NYHA = New York Heart Association. *Follow-up data were collected in 931 patients.

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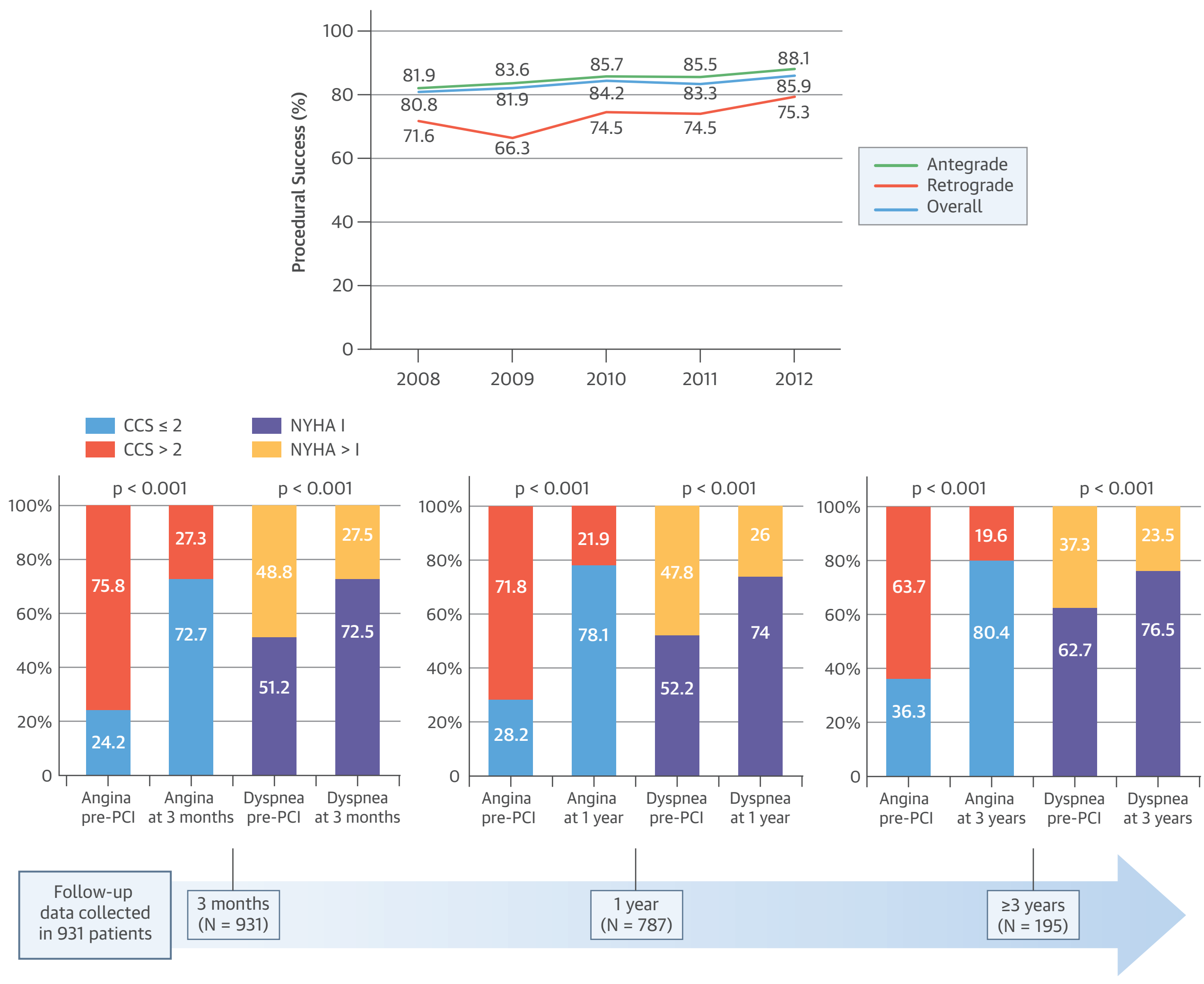
CENTRAL ILLUSTRATION **Retrograde CTO PCI in Europe**



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Increased success rate, good long-term outcomes, and reduction in symptoms. CTO = chronic total obstruction; PCI = percutaneous coronary intervention.

more likely to be adherent to follow-up. Data regarding collateral route and crossing technique were missing in some cases. Finally, angiographic dependent and clinical outcomes were not independently adjudicated.

CONCLUSIONS

Our study shows that among dedicated European operators, retrograde CTO PCI is performed extensively and is associated with favorably high success and low complication rates. Moreover, successful retrograde CTO PCI was associated with favorable long-term clinical outcomes and symptom alleviation (**Central Illustration**).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A retrograde approach to myocardial revascularization in patients with CTOs, when performed by experienced operators, can enhance the success of PCI.

TRANSLATIONAL OUTLOOK: More work is required to develop better criteria for the selection of patients for retrograde recanalization of coronary arteries with CTOs, on the basis of lesion characteristics.

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KEY WORDS chronic total occlusions, J-CTO score, retrograde PCI revascularization

APPENDIX For a list of participating centers, supplemental tables, and a figure, please see the online version of this article.