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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)

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ABSTRACT

OBJECTIVES This study sought to accurately describe the success rate, risks, and patient-reported benefits of contemporary chronic total occlusion (CTO) percutaneous coronary intervention (PCI).

BACKGROUND In light of the evolving techniques to successfully revascularize CTO lesions, there remains a compelling need to more accurately quantify the success rates, risks, and benefits of these complex procedures.

METHODS Using a uniquely comprehensive, core-lab adjudicated, single-arm, multicenter registry of 1,000 consecutive patients undergoing CTO PCI by the hybrid approach, we evaluated the technical success rates, complication rates, and raw and adjusted health status benefits at 1 month among successfully as compared to unsuccessfully treated patients.

RESULTS Technical success was high (86%). In-hospital and 1-month mortality was 0.9% and 1.3%, respectively, and perforations requiring treatment occurred in 48 patients (4.8%). Among those who survived and completed the 1-month interview ($n = 947$), mean ± SEM Seattle Angina Questionnaire quality of life scores improved from 49.4 ± 0.9 to 75.0 ± 0.7 ($p < 0.01$), mean Rose Dyspnea Scale scores improved (decreased) from 2.0 ± 0.1 to 1.1 ± 0.1 ($p < 0.01$), and physician health questionnaire (for depression) scores improved (decreased) from 6.2 ± 0.2 to 3.5 ± 0.1 ($p < 0.01$) at 1 month. After adjusting for baseline differences the mean group difference in Seattle Angina Questionnaire quality of life between successful and unsuccessful CTO PCI was 10.8 (95% confidence interval: 6.3 to 15.3; $p < 0.001$).

CONCLUSIONS Clarifying the success rates, risks, and benefits of CTO PCI will help to more accurately contextualize the informed consent process for these procedures so that patients with appropriate indications for CTO PCI can more effectively share in the decision to pursue this or other therapeutic options. (J Am Coll Cardiol Intv 2017;10:1523–34)

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ABBREVIATIONS AND ACRONYMS

AUC = appropriateness use criteria

AWE = antegrade wire escalation

CABG = coronary artery bypass graft

CI = confidence interval

CTO = chronic total occlusion

JCTO = Japanese chronic total occlusion

MI = myocardial infarction

PCI = percutaneous coronary intervention

PHQ = Physicians Health Questionnaire

QoL = quality of life

RDR = retrograde dissection and re-entry

SAQ = Seattle Angina Questionnaire

Patients with chronic total occlusions (CTO) of a coronary artery represent a complex and common clinical conundrum among patients with ischemic heart disease. In recent years, there has been a renewed and intense interest in the field of CTO percutaneous coronary intervention (PCI) (1), driven in large part by the dissemination of advanced CTO PCI techniques and teaching methods that are associated with improved technical success and acceptable procedural complication rates (2–6). Because these technical advances have expanded treatment options to a broader population of operators and patients with CTO, there is a compelling need to more accurately quantify the success rates, risks, and benefits of these complex procedures. Moreover, whereas the primary goal of CTO PCI is often to improve the patient's symptoms, strikingly little is known about health status (patient's symptoms, function, and quality of life [QoL]) recovery after contemporary CTO PCI.

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The OPEN-CTO (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures) study was designed to address the methodological limitations of prior studies of CTO PCI, including efforts to ensure consecutive enrollment, complete and systematic reporting of adverse events, and comprehensive health status assessments before and after CTO PCI. The key insights into the success rates, risks, and health status outcomes of contemporary CTO PCI will serve as the basis for more accurate informed consent for these procedures.

METHODS

PARTICIPATING CENTERS AND PATIENT POPULATION. OPEN-CTO is an investigator-initiated, multicenter, prospectively collected, observational registry of consecutive CTO patients undergoing PCI at 12 U.S. centers. All patients scheduled for a CTO PCI by an experienced CTO operator familiar with the hybrid strategy (1) at each participating hospital were screened for possible inclusion (age >18 years, negative pregnancy status for women, and ability to comply with telephone follow-up). Informed consent was obtained from every participant and each institution's own institutional review board approved the study.

CTO was defined as a 100% occlusion with antegrade intraluminal TIMI (Thrombolysis In Myocardial Infarction) flow grade of 0 and clinical or angiographic evidence of occlusion duration >3 months. The health status and clinical follow-up interviews were performed by a centralized call center without the capacity to translate, thus non-English-speaking patients and those unable to participate in the baseline or follow-up interview (e.g., those incarcerated, demented, or deaf) were excluded.

A limitation of published reports of CTO PCI has been the possibility of selective inclusion of patients that could bias to better outcomes. Accordingly, a unique feature of OPEN-CTO is a linkage to the NCDR

served on the Scientific Advisory Boards of Boston Scientific and Abbott Vascular; and has received honoraria from Boston Scientific and Abbott vascular for CTO proctoring. Dr. Cohen has received institutional research grant support from Boston Scientific, Abbott Vascular, and Medtronic; and has received consulting fees from Medtronic and Abbott Vascular. Dr. Lombardi has received speaking fees and honoraria from Boston Scientific, Abbott Vascular, and Abiomed; has received consulting fees from Vascular Solutions, Abbott Vascular, Boston Scientific, Abiomed, and Roxwood Medical; has equity in Roxwood Medical and Bridgepoint Medical; and his wife is an employee of Spectranetics. Dr. McCabe has received consulting fees from Abiomed. Dr. Karmpaliotis has received speaking fees, honoraria, and consulting fees from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Nicholson has received speaking fees and honoraria from Boston Scientific and Abbott Vascular. Dr. Pershad has received speaking fees and honoraria from Boston Scientific, Medtronic, Asahi Intecc, Edwards Lifesciences, and Abiomed; and has received consulting fees from Abiomed and Boston Scientific. Dr. Wyman has received speaking fees, honoraria, and consulting fees from Boston Scientific and Abbott Vascular. Dr. Spaedy has received speaking fees and honoraria from Boston Scientific and Abbott Vascular. Dr. Cook has received speaking fees and honoraria from Boston Scientific and Abbott Vascular. Dr. Doshi has received speaking fees and consulting fees from Boston Scientific and Abbott Vascular; has received consulting fees from Cardiovascular Systems Inc., Medtronic, and Spectranetics; and has received research grants from Boston Scientific. Dr. Federici has received honoraria from Boston Scientific. Dr. Thompson is an employee of Boston Scientific, Inc. Dr. Marso has received speaking fees and honoraria from Boston Scientific and Abbott Vascular. Dr. Spertus has received research grants from Lilly and Abbott Vascular; has served as a consultant for Novartis, Amgen, Bayer, and United Healthcare; owns the copyright to the Seattle Angina Questionnaire; and has an equity interest in Health Outcomes Sciences. Dr. Grantham has received speaking fees and honoraria from Boston Scientific, Abbott Vascular, and Asahi Intecc; has received institutional research grant support from Boston Scientific; has received institutional educational grant support from Abbott Vascular, Vascular Solutions, Boston Scientific, and Asahi Intecc; and is a part-time employee of Corindus Vascular Robotics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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(National Cardiovascular Disease Registry) Cath/PCI registry for auditing of enrollment. The success of consecutive enrollment has been previously reported and no case selection, other than adherence to inclusion and exclusion criteria, was identified (7).

The clinical indication for CTO PCI was determined and documented by the operator prior to the procedure. The appropriateness was assessed by the operator using the Society for Cardiac Angiography's appropriate use criteria (AUC) (8) for coronary revascularization mapping tool (9). When risk was not specifically qualified as high, intermediate, or low on the imaging or stress test report (68% of studies), the operators were required to estimate the risk.

TREATMENT ALGORITHM. The hybrid approach to CTO PCI entails a flexible approach that includes both antegrade and retrograde and luminal and subintimal lesion crossing techniques, has previously been described in detail, and has that has been shown to be safe and associated with high success rates in a multicenter registry (1). All operators enrolling in the OPEN-CTO trial received training in the hybrid approach and had performed over 100 cases using this method. One or more of 4 possible CTO, crossing strategies were employed in a sequence determined by the hybrid algorithm. Antegrade wire escalation (AWE) was performed with wires of increasing tip load, varying lubricity, and with the use of a microcatheter. Antegrade dissection and re-entry was performed with either a microcatheter and a knuckled wire or the Crossboss catheter (Boston Scientific, Marlborough, Massachusetts) for dissection followed by re-entry with the Stingray balloon (Boston Scientific) and wire system. Retrograde wire escalation was performed after collateral crossing with a microcatheter followed by use of the same wire escalation sequence as AWE, and retrograde dissection and re-entry (RDR) was performed after collateral crossing and by employing a knuckled wire for dissection, followed by the reverse controlled antegrade and retrograde tracking technique (RCART) for re-entry (10).

BASELINE AND FOLLOW-UP DATA COLLECTION. Baseline data collection was performed by on-site research nurses who were trained by the project coordinator. An experienced, centralized call center with staff trained in health status interviewing techniques performed all follow-up assessments at 1 month. In addition to a detailed health status assessment, patients were queried about current medication, medication discontinuance and reason, and rehospitalization events and their causes. Patient-reported health status was captured using the Seattle Angina Questionnaire (SAQ) (11), the Rose Dyspnea Scale (12), and the Patient Health Questionnaire (PHQ) 8 (13). The rationale for using these established health status instruments is summarized in the methods paper for OPEN-CTO (7).

All procedural angiograms were reviewed by a central angiographic core laboratory (Saint Luke's Mid America Heart Institute, Kansas City, Missouri) using QAngio XA 7.3 (Medis Medical Imaging Systems, Leiden, the Netherlands) software.

DEFINITIONS. Technical success was assessed by the angiographic core laboratory and was defined as the positioning of a guidewire in the distal true lumen of the first CTO attempted, deployment of a balloon or stent with final antegrade TIMI flow grade 2 or 3, residual stenosis $<50\%$ by angiographic core lab analysis, and no significant side branch occlusion. Operator-defined technical success was based on the same definition but relied on the operator's assessment of final TIMI flow grade, residual stenosis, and side branch occlusion. A significant side branch was defined as a branch supplying the left ventricle (including diagonal, posterolateral, posterior descending, obtuse marginal, and septal branches) that was $\geq$1.5 mm in diameter (14). Procedural success was defined as technical success and no major adverse cardiac or cerebrovascular events. Procedural major cardiac and cerebrovascular events were defined as in-hospital death, procedure-related myocardial infarction (MI), emergent coronary artery bypass graft (CABG), stroke, or clinically significant perforation. Periprocedural MI was defined according to the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation task force for the redefinition of MI, specifically types 4a and 5 (PCI-related and CABG-related MI, respectively) (15). Acute kidney injury and bleeding definitions are cited in the methods paper (7). Angiographic perforations were classified according to the Ellis criteria (16). Procedure time was defined as the time between local anesthetic injection and removal of the last guide catheter. Device time was defined as the time between local anesthetic injection and insertion of the first CTO device into the guide catheter. This time included the time to set up the procedure typically including sheath and guide insertion, angiography, procedural planning, and non-CTO PCI when indicated. CTO devices included guidewires, microcatheters, balloons, and the Crossboss catheter. First strategy switch time was defined as the time interval from device to the time when the operator declared the first strategy switch. Second strategy switch was defined as the time between the first strategy switch

and the time when the operator declared a change to the second strategy. Completeness of revascularization was assessed and reported by the operators' clinical (e.g., stress test results) and angiographic information. Thirty-day rehospitalization was ascertained by patient report during the 1-month telephone follow-up call.

STATISTICAL CONSIDERATIONS. Continuous variables are summarized as means ± SD and categorical variables are summarized as percentages. Baseline characteristics and clinical outcomes were compared between groups (successful vs. unsuccessful procedure) using the Student *t* test for continuous variables and chi-square or Fisher exact test for categorical variables. Observed-expected ratios for mortality with PCI were calculated by entering each patient into the NCDR risk prediction model (17) to calculate the expected mortality and then dividing the total number of observed deaths by the sum of expected mortalities for the entire population. Similarly, the predicted mortality with CABG was calculated using the Society of Thoracic Surgeons risk prediction model (18).

One-month health status outcomes were compared between patients undergoing successful versus unsuccessful CTO PCI. These analyses were restricted to those patients who underwent single-vessel CTO PCI and had no other treated lesions. Outcomes between groups were compared using propensity score matching to adjust for baseline demographic and clinical factors. For these analyses, we first developed a nonparsimonious logistic regression model to predict successful CTO PCI using the following variables: age, sex, race, education, finances, difficulty getting care, PHQ-8 score, body mass index, prior MI, prior CABG, hypertension, diabetes, smoking status, pre-procedure creatinine, LV systolic function, procedural complexity as assessed by the Japanese Chronic Total Occlusion (JCTO) score (19), CTO vessel location, and lesion length. Patients with successful and unsuccessful CTO PCI were then matched based on these propensity scores using optimal matching. Standardized differences in these factors before and after matching were calculated to assess balance. Finally, the effect of successful PCI for a CTO on 1-month SAQ outcomes was estimated adjusting for baseline SAQ score and any variables that were not balanced after propensity matching (standardized difference >10%). All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, North Carolina). A p value ≤0.05 was considered statistically significant.

Missing data were imputed using sequential regression imputation, conditioning on all variables used in the regression analysis, as well as baseline and follow-up SAQ scores (20). Follow-up SAQ QoL scores were obtained in 89% at 1 month.

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RESULTS

PATIENT CHARACTERISTICS, INDICATIONS, AND APPROPRIATENESS OF THE PROCEDURES. A total of 1,000 patients were enrolled and 1,054 CTO lesions were attempted between January 21, 2014, and July 22, 2015. The patient characteristics of the entire study population are summarized in **Table 1**. The patients were predominantly male, frequently diabetic (41%), more than one-third had undergone a prior CABG (37%), and 1 in 5 (21%) were previously attempted and failed. The most common indication for CTO PCI was symptom relief (**Figure 1A**). Seventy-two percent of those presenting with stable angina were classified as severe (Canadian Classification System class III or IV) angina. Among those patients with a stress test prior to the procedure (n = 782), 41% were reported or estimated by the operator to be high risk, whereas only 45 (8%) were low risk. High risk stress tests were more frequent when abstracted from the report as compared to those whose risk was estimated by the operator (59% vs. 30%; $p < 0.001$). Among patients whose procedures could be mapped to the AUC (n = 807), 60% were considered "appropriate," 20% "may be appropriate," and only 1% "rarely appropriate" (**Figure 1B**).

ANGIOGRAPHIC CHARACTERISTICS. The angiographic features of the first CTO lesion attempted are summarized in **Table 2**. The majority of lesions were in the right coronary artery (61.5%), were de novo (89.3%), and almost one-half were complex, as defined by a JCTO score >2. Mean occlusion length was 29 mm and calcification was present in 33% of lesions. Thirty-five percent of the CTO vessels were previously grafted and the majority of those grafts (74%) were totally occluded.

SUCCESS RATES IN OPEN-CTO. Using the core lab-adjudicated definition of success for the first CTO attempted, the technical success rate was 86% (**Table 3**). When technical success was determined by the operator without core lab data, the reported success rate was 90% (k = 0.77 vs. core lab definition).

TABLE 1 Baseline Patient Characteristics of the Entire Cohort (N = 1,000)

Age, yrs	65.4 ± 10.3
Sex	
Male	804 (80.4)
Female	196 (19.6)
White/Caucasian	902 (90.2)
Body mass index, kg/m^2	30.5 ± 6.0
Hypertension	852 (85.5)
Total cholesterol, mg/dl	156.9 ± 49.9
Diabetes	412 (41.2)
History of chronic kidney disease	135 (13.5)
History of smoking	638 (64.5)
Current smoker	133 (13.4)
Chronic obstructive pulmonary disease	144 (14.4)
Previous myocardial infarction	484 (48.4)
Previous bypass	365 (36.5)
Previous angioplasty	656 (65.7)
Previous stroke	77 (7.7)
Peripheral artery disease	175 (17.5)
Ejection fraction, % (n = 750)	51.0 ± 13.8
Ejection fraction <35% (n = 750)	103 (13.7)
Atrial fibrillation	153 (15.3)
Type of angina (missing n = 7)	
None	88 (8.8)
Stable	832 (83.2)
Unstable angina/acute coronary syndrome	73 (7.3)
Stable angina: CCS classification (missing n = 1)	
I	35 (4.2)
II	195 (23.4)
III	473 (56.9)
IV	129 (15.5)
Unstable angina: TIMI risk score	
Low, 0–2	3 (4.1)
Intermediate, 3–4	35 (47.9)
High, >5	35 (47.9)
Noninvasive test performed	793 (80.1)
Mortality risk reported on noninvasive study	307 (38.3)
Low	23 (7.5)
Intermediate	104 (33.9)
High	180 (58.6)
Mortality risk estimated by operator	522 (65.8)
Low	48 (9.2)
Intermediate	315 (60.3)
High	159 (30.5)

Values are mean ± SD or n (%).
CCS = Canadian Cardiovascular Society; TIMI = Thrombolysis In Myocardial Infarction.

The procedural success rate was 81% and 85% using the core lab and operator definitions, respectively.

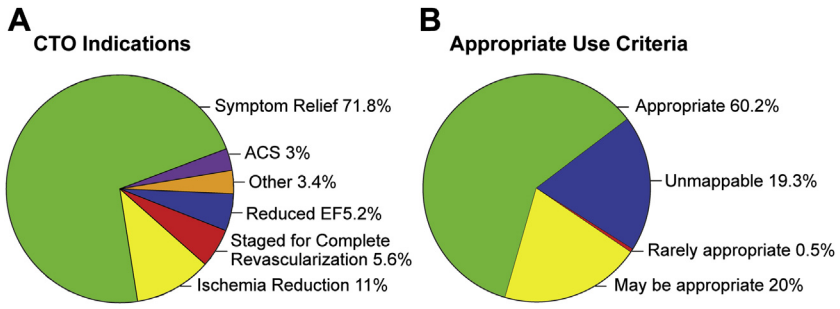
HYBRID PROCEDURAL DETAILS. The sequence of strategies, and the successful strategy used are depicted in Figure 2. AWE was the most frequent first strategy (Figure 2A), followed by RDR and the initial approach to the first CTO attempted was successful 56% of the time (Table 3). The most successful first strategy was RDR (62% success rate) followed by AWE (59% success rate). When the first strategy was unsuccessful (439 cases) a second strategy was employed in 97% of cases. When a second strategy was employed, ADR was most frequently selected (43%) (Figure 2B). The mean time to switching from the first to the second strategy was 30 ± 25 min (range 3 to 132 min) (Table 3). When used, the second strategy was successful in just over one-half of attempts (52%). More than 2 strategies were employed in 17% of cases. Overall, AWE accounted for most of the successes (41% of successful strategies) (Figure 2C), followed by RDR (25%) and ADR (24%).

PROCEDURAL COMPLICATIONS. In-hospital procedure-related major cardiac and cerebrovascular events are summarized in Table 4. In-hospital death occurred in 9 patients (0.9%). All of the deaths were associated with a complication; 9 had a perforation requiring treatment, 2 of whom also experienced periprocedural MI. Four of the fatal perforations occurred among subjects with a history of prior CABG (1.1%) and 5 fatal perforations occurred among non-CABG patients (0.8%; p = 0.62). Assuming that all procedures were elective, the expected mortality using the NCDR risk prediction tool (which does not include a covariate for CTO PCI) was 0.4% yielding an observed to expected ratio of 2.3. The Society of Thoracic Surgeons predicted risk of mortality with CABG among the entire OPEN-CTO cohort of patients was 1.7%.

Overall perforations were observed by the core lab in 88 participants (8.8%). The perforations were most frequently located in the CTO vessel (88%) and characterized as Ellis class II (50%). Among those that occurred in the CTO vessel, 37 (48%) were identified prior to stent deployment and 40 (52%) were identified after stent deployment. Among those perforations identified by the core lab, 42 (48%) were characterized as clinical perforations. Six additional clinical perforations were reported by the operators but not identified by the core lab because angiographic images of the perforation were not captured. Periprocedural MI was observed in 26 (2.6%) and in-hospital repeat PCI occurred in 1 (0.1%). Overall 7 patients (0.7%) were referred for emergent surgery and no in-hospital strokes were identified. Acute kidney injury was identified in 8 (0.8%), and there were 3 (0.3%) major bleeding events that required treatment.

CLINICAL AND HEALTH STATUS OUTCOMES. One month clinical and health status follow-up were available for 947 patients (94.7%). Thirteen (1.3%)

FIGURE 1 Distributions of the Indications for and Appropriateness Ratings of the Procedures



Distributions of the indications **(A)** for and appropriateness ratings **(B)** of the procedures. ACS = acute coronary syndrome; CTO = chronic total occlusion; EF = ejection fraction.

were deceased (9 in hospital and 4 after discharge), 29 (0.3%) refused the follow-up interview, 3 (0.03%) were not reached due to inadequate contact information, and 8 (0.8%) were too ill to complete the interview. Overall, 137 patients (14.8%) reported 1 or more rehospitalizations, and the majority were unplanned (89%). The most common reason for rehospitalization was chest pain (19%).

EARLY HEALTH STATUS RESPONSES TO CTO PCI. Among the 991 patients discharged alive, 890 (89%) had complete data on health status at both baseline and 1 month. All of the SAQ score domains, the Rose Dyspnea Scale, and the PHQ-8 scores improved significantly after CTO PCI (Figure 3). Mean ± SEM SAQ QoL scores improved from 49.4 ± 0.9 to 75.0 ± 0.7 ($p < 0.01$), mean Rose Dyspnea Scale scores improved (decreased) from 2.0 ± 0.1 to 1.1 ± 0.1 ($p < 0.01$), and PHQ-8 scores improved (decreased) from 6.2 ± 0.2 to 3.5 ± 0.1 ($p < 0.01$) at 1 month.

The patient and procedural characteristics of the patients who underwent single-vessel CTO PCI divided into successful (n = 592) and unsuccessful (n = 88) procedures are summarized in Table 5. Patients with successful procedures had lower serum creatinine levels and were less likely to have diabetes or prior CABG. Successfully treated patients more frequently had septal collaterals and had a larger mean distal vessel diameter. The mean

TABLE 2 Angiographic Characteristics of the Entire Cohort (N = 1,000)

Total number of CTO vessel attempted	1,054
First attempted CTO vessel location	
Right coronary artery	615 (61.5)
Left anterior descending	207 (20.7)
Left circumflex	170 (17.0)
Left main	8 (0.8)
First attempted CTO lesion characteristics	
De novo	893 (89.3)
In-stent restenosis	107 (10.7)
Lesion length, mm	61.0 ± 28.5
Occlusion length, mm	29.1 ± 23.8
Japanese CTO score	2.3 ± 1.3
Japanese CTO score >2	468 (46.8)
Distal reference vessel diameter, mm	3.3 ± 0.6
First attempted CTO vessel collaterals present	880 (88.4)
Septal collaterals	753 (86.2)
Epicardial collaterals	238 (26.8)
Bridging collaterals	88 (8.9)
First attempted CTO vessel previously grafted	349 (34.9)
Graft to CTO patent	91 (26.1)
Graft used in case	75 (21.5)

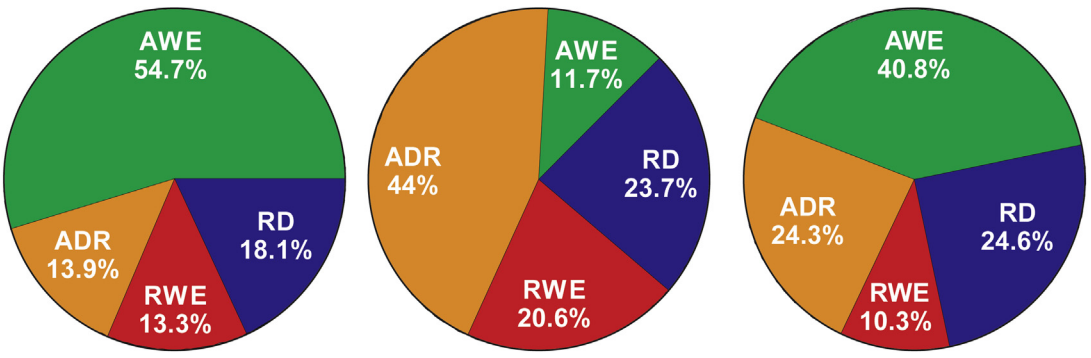
Values are n (%) or mean ± SD.
CTO = chronic total occlusion.

TABLE 3 Procedural Details of the Entire Cohort (N = 1,000)

Overall technical success rate, core lab	862 (86.2)
Overall technical success, physician-reported	900 (90)
Total procedural time, min	120.7 ± 64.4
Device time, min	24.0 ± 24.9
Crossing time, min	69.6 ± 50.7
Total fluoroscopy time, min	50.4 ± 34.1
Total radiation air kerma dose, Gy	2534.0 ± 1884.2
Total contrast dose, cc	262.0 ± 139.5
First strategy attempted	1,000
Technical success rate	561 (56.1)
Switch time	30.5 ± 25.3
Second strategy attempted	439
Technical success rate	228 (51.9)
Switch time	40.9 ± 85.1

Values are n (%) or mean ± SD.

FIGURE 2 First, Second, and Successful Strategies Employed During Hybrid CTO PCI



First **(A),** second **(B)**, and successful **(C)** strategies employed during hybrid chronic total occlusion (CTO) percutaneous coronary intervention (PCI). ADR = antegrade dissection and re-entry; AWE = antegrade wire escalation; RDR = retrograde dissection and re-entry; RWE = retrograde wire escalation.

JCTO scores were similar between successful and unsuccessful groups, as were the frequency of JCTO scores >2. Successful procedures were associated with higher rates of complete revascularization and had lower procedure time, radiation dose, and contrast dose.

Table 6 depicts health status scores at baseline and 1 month, and the mean change from baseline to 1 month among the successful and unsuccessful groups. Baseline health status scores were similar between groups. Both groups reported improvements in every domain measured. Compared with the unsuccessful group, the successful group scores improved more than the unsuccessful group scores did. After adjusting for baseline differences in patient, procedural, and baseline health status characteristics, successful CTO PCI was associated with greater health status improvement than unsuccessful CTO PCI. The greatest difference in SAQ scores was seen in the QoL domain where we observed a 10.8 (95% confidence interval [CI]: 6.3 to 15.3) point greater improvement among successful versus unsuccessful procedures ($p < 0.001$). To assess the impact of missing data on our observations, we imputed all missing SAQ data to 0 and the results were not different. Dyspnea scores (adjusted mean difference: −0.6 points; 95% CI: −0.9 to −0.3 points; $p < 0.001$) and depression scores (adjusted mean difference: −1.9 points; 95% CI: −2.8 to −1.4; $p < 0.001$) also improved significantly more often after successful than unsuccessful procedures.

DISCUSSION

The growing feasibility of CTO PCI, especially with a hybrid approach that includes the flexible implementation of up to 4 crossing strategies executed in a sequence that is determined by the

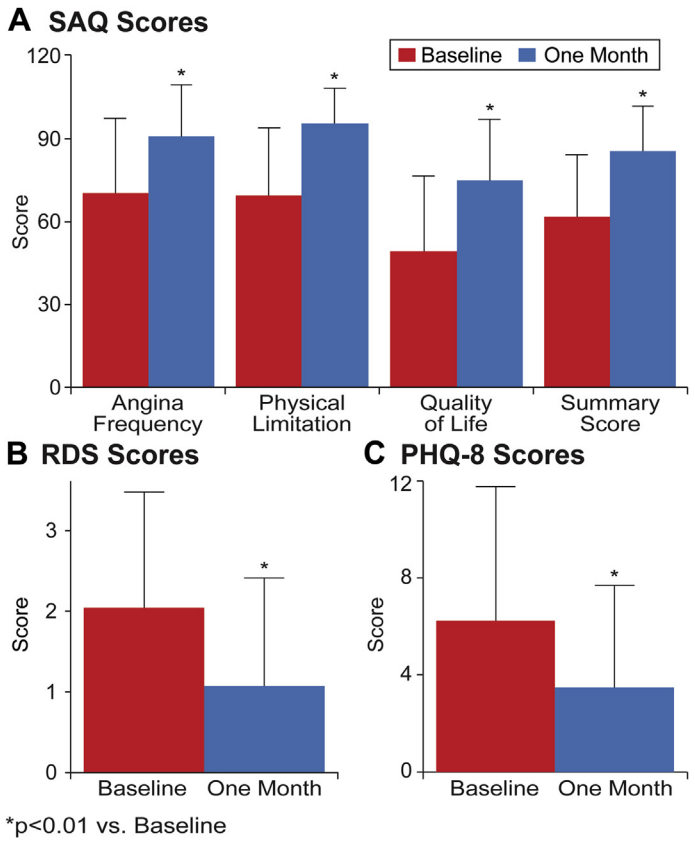
TABLE 4 In-Hospital Complications of the Entire Cohort

MACCE	70 (7.0)
Death	9 (0.9)
Myocardial infarction	26 (2.6)
Stroke	0 (0.0)
Emergent surgery	7 (0.7)
Clinical perforation	48 (4.8)
Repeat PCI	1 (0.1)
Perforation	88 (8.8)
Ellis grade 1	11 (12.5)
Ellis grade 2	44 (50.0)
Ellis grade 3	28 (31.8)
Ellis grade 3 cavity spilling	5 (5.7)
Perforation location	
CTO vessel	75 (85)
Non-CTO vessel	3 (3.4)
Collateral	8 (9.1)
Septal	3 (37.5)
Epicardial	5 (62.5)
Bleeding requiring treatment	3 (0.3)
Access site hematoma	43 (4.3)
Acute kidney injury	5 (0.7)

Values are n (%).

CTO = chronic total occlusion; MACCE = major adverse cardiac and cerebrovascular events; PCI = percutaneous coronary intervention.

FIGURE 3 Unadjusted Health Status Scores at Baseline and 1 Month



Unadjusted mean ± SEM health status scores at baseline and 1 month among those with paired data (n = 890). PHQ-8 = Physicians Health Questionnaire 8; RDS = Rose Dyspnea Scale; SAQ = Seattle Angina Questionnaire.

angiographic characteristics of the occlusion, mandates a thorough evaluation of its success, risks, and impact on outcomes. We report the results of a comprehensive and methodologically rigorous registry to more accurately describe the outcomes of contemporary CTO PCI using the hybrid approach. We observed highly appropriate case selection for coronary revascularization as judged by the American College of Cardiology/American Heart Association's AUC methodology and observed only a modest disparity between core lab-adjudicated and physician-reported outcomes. Overall, the success rate was high (86%) albeit with major complication rates that were higher than those observed for PCI of non-CTO lesions. Importantly, we observed substantial improvements in patient-reported health status after treatment, which was significantly greater following successful than unsuccessful procedures.

PATIENT SELECTION FOR CTO PCI. The results of the NCDR-based audit of enrollment are published elsewhere (7) and confirm that these patients were consecutively enrolled, thus minimizing potential selection biases in this report. This is particularly important as case selection or "cherry picking" easier or uncomplicated cases to enroll in unaudited, self-reported registries could result in overestimation of success and under-reporting of adverse events relative to real world, every day CTO PCI that occurs at these expert centers. The majority of patients (72%) were selected with the primary goal of providing symptom relief, which is reflected in the high rate of "appropriate" and "may be appropriate" indications for revascularization. The rates of rarely appropriate (0.5%) and unmappable (19%) AUC ratings in OPEN-CTO compare favorably with the AUC indications in recently published elective PCI cohorts (21,22), where rates of "rarely appropriate" indications for revascularization were 12% to 14% among patients with less complex disease. The very low incidence of "rarely appropriate" ratings based on AUC criteria are likely a reflection of the anatomical complexity of disease in this population, their high symptom burden, and the frequency of high risk stress tests. One in 5 of these patients were referred to CTO PCI "experts" after prior failed procedures, which may also serve as a filtering mechanism for more appropriate cases. Alternatively, the very low "rarely appropriate" rates in OPEN-CTO may be due to operator overestimation of symptom severity or noninvasive imaging-based risk assessment. However, we confirmed significant symptom burden on baseline patient-reported health status scales (mean baseline SAQ QoL scores: 49.5 ± 27.5) and also noted the physician-estimated risk of noninvasive studies often underestimated rather than overestimated risk classification. This suggests that "gaming" the AUC designation by up-coding symptoms and stress test risk does not explain the low frequency of inappropriate ratings.

SUCCESS RATES IN CTO PCI. Using our primary prespecified definition of success (core lab-defined final TIMI flow grade ≥2, residual stenosis <50%, and no loss of a major side branch), we observed a technical success rate of 86%. This success rate is numerically lower than recently published rates for hybrid CTO PCI (91%) (5). The difference in success rates between our study and others may reflect our methods (NCDR audit and core lab analysis), different operators, different definitions, or may simply have been related to chance. One such difference is our inclusion of the absence of a side branch occlusion. When we eliminated the side branch occlusion component of our

success definition, our technical success rate in OPEN-CTO increased to 87%, which is still numerically lower than those observed in other studies of hybrid CTO PCI but similar to the European hybrid report (6) where a more restrictive definition of success was used (final TIMI flow grade 3, residual stenosis <30%). Furthermore, we defined success based on the result of the first attempt of the first CTO in the first CTO PCI setting, whereas others report success after reattempt in a second setting. When we asked operators to report success without the angiographic core lab data, they reported a success rate of 90%, which is more in line with previous physician-reported estimates. Taken together, these observations suggest that operators tend to overestimate success rates relative to more rigorously adjudicated core lab analyses. This has important implications in the informed consent process and in the design and evaluation of CTO PCI trials, particularly those done for new technological development where core lab analysis is frequently required.

COMPLICATIONS ASSOCIATED WITH CTO PCI. The risks of CTO PCI are reported to be decreasing over time (23) and similar to non-CTO PCI. Our observed mortality was 0.9%, which is numerically higher than was previously reported in both hybrid and nonhybrid treated cohorts (4,6,24). The observed mortality rate in OPEN-CTO is not higher than that described in other "high risk" interventions, for example, degenerative saphenous vein graft PCI where in-hospital mortality was described as "rare" at 1.1% (25). We further contextualized this observed mortality rate by calculating patients' predicted mortality using the NCDR risk prediction model. Mortality for CTO PCI was 2.3-fold higher than the predicted mortality for non-CTO lesions, because the NCDR mortality model explicitly excluded CTO procedures from the development of its risk model (17). This is important because CTO PCI continues to be a specialized procedure at many centers where a limited number of operators perform a disproportionate number of these higher risk procedures. With the increasing frequency of CTO PCI in the NCDR (26) revisions to the model, including CTO appears justified so that interventionalists who are willing to offer these procedures to well-informed patients with an appropriate clinical indication are not unfairly scrutinized by physician-specific outcome reporting.

Perforations were observed by the core lab in 8.8% of cases and were reported by operators in 6.6% of cases. The observed disparity between operator-reported and core lab-identified perforation rates is difficult to completely reconcile. Nonetheless, the frequency of perforation and clinical perforation is higher than previously reported by both hybrid and nonhybrid operators (23). The higher frequency of perforation we observed may relate to the implementation of core lab assessment where physician under-reporting is overcome as there may be a tendency for operators to not report clinically

TABLE 5 Patient, Lesion, and Procedural Characteristics for the Comparison of Health Status According to Procedure Success Among Patients With Single-Vessel Disease

	Successful (n = 592)	Unsuccessful (n = 88)	p Value
Patient characteristics			
Age, yrs	65.4 ± 9.9	67.1 ± 8.8	0.113
Male	461 (77.9)	77 (87.5)	0.038
White/Caucasian	533 (90.0)	79 (89.8)	0.939
Body mass index, kg/m^2	30.5 ± 6.1	29.5 ± 4.8	0.171
Hypertension	494 (84.2)	79 (90.8)	0.104
Diabetes mellitus	229 (38.7)	45 (51.1)	0.026
Chronic kidney disease	73 (12.3)	14 (15.9)	0.348
Chronic obstructive pulmonary disease	89 (15.0)	16 (18.2)	0.445
Myocardial infarction	272 (45.9)	45 (51.1)	0.362
Prior bypass surgery	182 (30.7)	44 (50.0)	<0.001
Prior angioplasty	396 (67.0)	63 (71.6)	0.391
Prior stroke or transient ischemic attack	54 (9.1)	8 (9.1)	0.992
Peripheral arterial disease	89 (15.0)	21 (23.9)	0.035
Ejection fraction, %	52.3 ± 13.2	50.1 ± 13.8	0.204
Lesion characteristics			
CTO vessel			0.627
Right coronary artery	381 (64.4)	58 (65.9)	
Left anterior descending	118 (19.9)	17 (19.3)	
Left circumflex	87 (14.7)	11 (12.5)	
Left main	6 (1.0)	2 (2.3)	
CTO lesion characteristics			0.842
De novo	422 (90.6)	63 (91.3)	
In-stent restenosis	44 (9.4)	6 (8.7)	
Lesion length, mm	61.2 ± 28.0	67.4 ± 29.7	0.059
Occlusion length, mm	28.2 ± 22.6	33.3 ± 26.8	0.064
Japanese CTO score	2.3 ± 1.3	2.4 ± 1.2	0.508
Japanese CTO score >2, %	271 (45.8)	44 (50.0)	0.458
Distal reference vessel diameter, mm	3.3 ± 0.6	3.0 ± 0.5	0.028
Collaterals present	528 (89.9)	77 (87.5)	0.482
Septal collaterals	464 (88.2)	60 (77.9)	0.012
Epicardial collaterals	141 (26.4)	24 (31.2)	0.378
Procedural characteristics			
Total procedural time, min	107.1 ± 59.0	150.4 ± 53.5	<0.001
Total fluoroscopy time, min	45.0 ± 34.2	65.9 ± 30.4	<0.001
Total radiation air kerma dose, Gy	2280.8 ± 1802.0	3335.5 ± 2164.8	<0.001
Total contrast dose, cc	241.9 ± 129.6	310.1 ± 153.2	<0.001
MACCE	34 (5.7)	9 (10.2)	0.106
Complete revascularization	541 (91.9)	15 (17.2)	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Tables 2 and 3.

TABLE 6 Comparison of Health Status Improvement According to Procedural Success Versus Failure

	Successful (n = 592)			Unsuccessful (n = 88)			Adjusted Between Group Difference (95% CI)*	p Value
Scale	Baseline	1 Month	Δ	Baseline	1 Month	Δ		
SAQ-AF	71.4 ± 26.4	91.9 ± 17.3	20.4 ± 25.2	68.3 ± 28.0	83.9 ± 26.3	15.6 ± 24.5	7.4 (3.6 to 11.2)	<0.001
SAQ-PL	64.7 ± 25.9	96.5 ± 11.3	27.1 ± 24.7	66.2 ± 25.8	90.1 ± 18.6	19.9 ± 25.7	6.5 (3.1 to 9.9)	<0.001
SAQ-QoL	49.7 ± 27.5	76.2 ± 21.4	26.6 ± 27.5	50.7 ± 27.7	66.0 ± 24.7	15.3 ± 25.1	10.8 (6.3 to 15.3)	<0.001
SAQ-SS	62.0 ± 22.3	86.6 ± 15.5	24.6 ± 21.0	61.5 ± 23.4	77.7 ± 20.4	16.1 ± 19.7	8.9 (5.6 to 12.1)	<0.001
RDS	2.1 ± 1.4	1.1 ± 1.3	−1.0 ± 1.4	2.1 ± 1.4	1.7 ± 1.5	−0.4 ± 1.4	−0.6 (−0.9 to −0.3)	<0.001
PHQ-8	6.5 ± 5.7	3.4 ± 4.1	−3.1 ± 5.3	6.3 ± 5.7	5.2 ± 5.1	−1.2 ± 4.9	−1.9 (−2.8 to −1.3)	<0.001

Values are mean ± SD unless otherwise indicated. *Between group difference is adjusted for the propensity of procedural success (see the methods for details).

AF = angina frequency; PHQ-8 = Physicians Health Questionnaire 8; PL = physical limitation; QoL = quality of life; RDS = Rose Dyspnea Scale; SAQ = Seattle Angina Questionnaire; SS = summary score; Δ = change between baseline and 1 month.

insignificant perforations to avoid scrutiny. The possibility that the techniques employed were causative cannot be dismissed and should be the focus of future investigation.

It should also be emphasized that perforation, tamponade, and death occurred with similar frequency among CABG and non-CABG patients. Among some interventionalists there is a sense that the pericardium is "adherent and protective" after CABG. This may be unfounded and our findings suggest that CTO operators should exercise the same restraint (e.g., when considering a tortuous epicardial collateral for crossing) and similar vigilance when pericardial staining is observed with post-CABG patients as they do with non-CABG patients.

HEALTH STATUS BENEFITS OF CTO PCI. Defining the benefits of PCI has, in general, been limited by the predominant use of physician-ascertained angina with the Canadian Classification System of angina. Efforts to define the benefits of CTO PCI using patient-reported outcome measures such as the SAQ have been limited. The use of such measures provides a unique perspective from the patient, without the potential influence of observer bias. The few studies that have used the SAQ have been limited by high loss to follow-up, single-center design (27,28), short-term follow-up (27), and a preponderance of non-CTO providers where case selection likely limited the applicability of the observations (29). The OPEN-CTO registry included comprehensive assessments of angina, angina equivalents such as dyspnea, and the impact of CTO PCI on patient outlook and depression, all of which are understudied potential benefits of CTO PCI. We found significant early improvements in every health status domain that was measured. We also identified significant differences between successful and unsuccessful procedures among patients undergoing single-vessel CTO PCI. These results are in keeping with those from the FACTOR (FlowCardia's Approach to Chronic Total Occlusion Recanalization) trial (30) and 2 other studies of health status outcomes after CTO PCI (27,29). Further studies are needed to examine the predictors of greater or lesser benefit to help identify optimal candidates for CTO PCI. However, we found a substantial improvement in early mean health status scores after unsuccessful CTO PCI. Such an increase in health status among patients with a failed procedure was not observed to this degree in the FACTOR trial. Whether this difference between the OPEN and FACTOR trials is related to unique procedural techniques (the use of the FlowCardia device vs. hybrid techniques such as dissection and re-entry), patient selection differences between a randomized trial and a real-world registry, the use of additional antianginal therapies after a failed procedure, the placebo effect, or other factors is unclear and will require further investigation.

STUDY LIMITATIONS. OPEN-CTO is a prospective real-world single-arm registry and not a randomized clinical trial. As such, the study provides no information on outcomes of patients with CTO who did not undergo PCI. Whereas OPEN was performed by 11 operators with varying experience in CTO PCI, these operators still represent a group of well-trained, high-volume operators with at least 2 years of hybrid CTO experience prior to enrolling in the trial. Thus, the results may not be translatable to less experienced and lower-volume CTO operators. Given the limited availability of some health status instruments in other languages, and the difficulty of conducting follow-up health status interviews in languages other than English, only patients who could speak English were included in OPEN CTO, which is consistent with prior registries. We did not mandate collection of cardiac biomarkers, creatinine, and hemoglobin after the procedures so the rates of periprocedural MI, acute kidney injury, and bleeding are likely to be underestimated. A prior study identified procedure-related

MI in 8.8% of cases, especially with the retrograde approach. These MI were associated with excess mortality at follow-up (31). Objective measurements of physical capacity, such as those from exercise stress testing were not systematically available in follow-up. However, given the significant correlation between SAQ physical limitation scores and exercise duration (11), the robust improvement in scores within this domain after successful CTO PCI underscores improvement in functional capacity.

CONCLUSIONS

In a comprehensive, core lab-adjudicated, single-arm, multicenter trial of 1,000 consecutive patients undergoing CTO PCI using the hybrid approach, operators achieved high technical success rates counterbalanced by complication rates that were higher than those described for non-CTO PCI. Patients with successful CTO PCI demonstrated significant health status benefits at 1 month. Clarifying the successes, risks, and benefits of CTO PCI will help to more accurately contextualize the informed consent process for these procedures so that appropriately selected patients can more effectively share in the decision to pursue PCI or other therapeutic options.

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PERSPECTIVES

WHAT IS KNOWN? CTO are commonly discovered and their treatment with PCI is increasing despite a paucity of accurate information on the safety and patient-reported benefits of this higher risk procedure.

WHAT IS NEW? Contemporary CTO PCI at 12 expert centers where selection bias did not occur was highly appropriate by AUC but was associated with higher than expected perforation rates and significant health status benefits.

WHAT IS NEXT? The identification of higher than previously reported complications in CTO PCI underscores the need not only for caution among operators, but also for technique and device development that enhance the safety of these procedures.

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