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Long-term clinical outcomes after successful and failed recanalization to native chronic Total occlusion: Insights from the Busan chronic Total occlusion (B-CTO) Registry☆

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ABSTRACT

Objective: To assess hard major adverse clinical events (HMACE) after successful versus failed percutaneous coronary intervention for chronic total occlusion (PCI-CTO).
Background: There are limited data regarding long-term HMACE risks based on PCI-CTO success.
Methods: First-time PCI was performed in 438 consecutive patients with 473 target CTO lesions. Patients after procedural success (n = 355; 378 CTO lesions) and failure (n = 83; 95 CTO lesions) were followed for an average 40 months (7–77 months range). We compared HMACE (composite of cardiac death, non-fatal myocardial infarction (MI), and stroke) dependent on the success of PCI.
Results: The incidence of HMACE was low, with a total of 16 events, and did not differ {6% vs.3.1%, HR = 0.47; CI [0.16–1.35; p = 0.162} dependent on the success of PCI-CTO. There were less cardiac deaths {0.3% vs. 1.2%, RR = 0.22; CI [0.01–3.50];p = 0.283}, non fatal MI {1.1% vs.3.6%, RR = 0.27; CI [0.06–1.22], p = 0.089}, but more strokes {1.7% vs.1.2%, RR = 1.32; CI [0.16–10.99], p = 0.795} after successful PCI-CTO.
Conclusions: The risks of HMACE after PCI-CTO over long-term follow-up were minimal, and do not depend on the procedure success. This unexpected finding somewhat challenge the aggressive interventional approach, and should be confirmed in the adequately powered randomized trial.

1. Introduction

Native chronic total occlusions (CTO) are the most complex and challenging coronary lesions for interventional cardiologists, while the CTO patients treated with percutaneous coronary interventions (PCI) are targeted infrequently (10–15%) [1–3]. likely due to historically low procedural success rates (up to 35% of failure), technical complexity, high equipment use, and risk of major periprocedural complications [4]. As compared with the failure, successful PCI-CTO may offer significant clinical benefits, such as improvement in angina, left ventricular function, potential survival advantages with a reduction for the need of CAGB [5–8]. However, the impact of recanalization success on hard major adverse clinical events (HMACE) is unclear in general, and in East Asians in particular. Therefore, the objective of the current observational study was to establish long-term HMACE in a prospective CTO registry in Busan, Korea (B-CTO).

2. Methods

2.1. Study population

A prospective, single-center B-CTO has been initiated in September 1999, and is currently open. The protocol for the registry was approved by the Institutional Ethics Committee of Dong-A University Hospital (Busan, Korea) and the overall study design and flow diagram are shown in Fig. 1.

We enrolled 438 consecutive patients with 473 target CTO lesions after excluding 27 cases (incomplete or terminated PCI). The entire pool of CTO lesions was divided into procedural success (n = 355 patients with 378 CTOs) and failure groups (n = 83 patients with 95 CTOs). The definition of native CTO was 100% occluded coronary segment with Thrombolysis In Myocardial Infarction (TIMI) flow grade of 0, longer than 3 months duration according to the consensus

☆ Dedicated to the late Professor Mitsudo, the Master CTO Interventionist, and Renowned Teacher and Friend.

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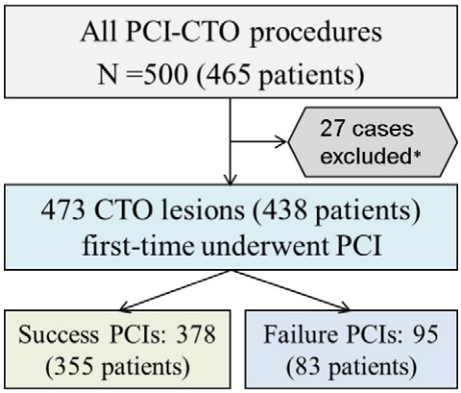

Fig. 1. Patient Flow and Overall Study Design. CTO: chronic total occlusion, PCI: percutaneous coronary intervention. *Due to premature PCI termination.

in EuroCTO club [9]. Duration was estimated based on the interval from the last episode of acute coronary syndrome (ACS), or in patients with no history of ACS from the first episode of exertional angina consistent with the location of the occlusion or previous coronary angiogram. Procedural success was defined as <20% residual stenosis with TIMI flow grade ≥ 2 by visual estimation of the angiograms as previously described [10]. We excluded patients presented with acute myocardial infarction within 4 weeks, cardiogenic shock; premature recanalization termination hemorrhagic diathesis; renal dysfunction (serum creatinine >2.5 mg/dl); and life expectancy <3 years.

2.2. PCI-CTO techniques

All patients were treated with aspirin, clopidogrel and initial bolus of intravenous unfractioned heparin (100 IU/kg) before PCI. The activated clotting time was maintained between 250 and 300 s, and monitored every 30 min. Glycoprotein IIb/IIIa inhibitors were permitted to use at the discretion of the interventional cardiologists.

The CTO guidewire strategies included the following: single-wire technique, parallel-wires technique and intravascular ultrasound-guided wiring technique, as well as retrograde wiring, including simple retrograde wiring, kissing wires, controlled antegrade retrograde tracking (CART) and reverse CART technique, as previously described [9]. The Rendezvous techniques applied after a retrograde guidewire was successfully crossed a CTO into the proximal true lumen [11].

2.3. Clinical outcomes and definitions

The primary outcome was the composite HMACE rate (cardiac death, non-fatal myocardial infarction, and stroke) during clinical follow-up. The outcome data were collected through outpatient clinic, hospital records, and telephone interviews.

2.4. Statistical analysis

All analyses were performed on an intention-to-treat basis, unless stated otherwise. A descriptive analysis was performed by presenting data as mean (standard deviation, SD)/median (interquartile range, IQR) or number (proportion). Continuous variables were compared with a t-test or Wilcoxon rank sum test, and categorical variables were compared with chi-square statistics or Fisher's exact test, as appropriate for the available data. The independent factors of PCI-CTO success were assessed in multivariate logistic regression analysis with a forward/backward elimination technique, and only candidate variables with a P value of less than 0.30 were selected for the final multivariate model. The association between the HMACE components and procedural success are expressed as adjusted odds ratio (OR) with 95% confidence intervals (CI). Hazard ratios (HR) and 95% CI estimated with Cox proportional-hazards model. The follow-up data were censored at the time of last contact or at 72 months. A two-tailed p-value of <0.05 was the criteria for statistical significance. All statistical analyses were performed using PASW Statistics software (version 18.0; SPSS Inc., Chicago, IL, USA), and the R programming language (R Foundation for Statistical Computing).

3. Results

3.1. Baseline characteristics

The background demographics and clinical characteristics of the B-CTO Registry are outlined in Table 1. Among all parameters only female gender has been associated with failed PCI-CTO. All other variables were not different dependent on revascularization success.

3.2. Clinical outcomes

Clinical follow-up data (median 40 months, interquartile range: 7 to 77 months) were obtained in all B-CTO patients. The HMACE rate was low with the total of 16 events, including 1 CV death in each arm. The occurrence of cardiac death (1.2% vs. 0.3%; HR: 0.22; 95% CI: 0.01 to 3.50), non-fatal MI (3.6% vs. 1.1%; HR: 0.27; 95% CI: 0.06 to 1.22) and stroke (1.2% vs. 1.7%; HR: 1.32; 95% CI: 0.16 to 10.99) were similar between successful and failed PCI. The details are outlined in Table 2.

4. Discussion

The present prospective, ongoing B-CTO Registry revealed low HMACE risks independent from the success of PCI-CTO. Importantly, the success rate for intervention was 80% with low occurrence of procedure-related complications. The major finding of our Registry was the fact that risks of HMACE after PCI-CTO over long-term follow-up were minimal, and, most intriguing, do not depend on the procedure success. This surprise finding should be confirmed in the adequately powered randomized trial. Obviously, yet unclear, compensatory mechanism to protect from failed CTO recanalization should be considered, and explored further somewhat challenging currently dominant aggressive interventional approach. Also, unexpected, was the fact that only female gender distinguished the recanalization success, while multiple conventional risk factors failed to triage and predict such adverse association.

The index data are consistent with several event-free survival observational studies [8,12,13], but contradict other evidence [14,15,16]. It seems the main reason for such discrepancy is a choice of MACE individual components. Usually, investigators apply much more liberal MACE including repeat revascularizations, urgent target vessel procedures, need for CABG, inter-procedural stent thrombosis, or other less hard components somewhat diluting clinical message. We deliberately applied the hardest-to-get classical clinical components to eliminate

Table 1
Baseline clinical characteristics.

	Failure (n = 83)	Success (n = 355)	P value
Age, years	62 ± 10	61 ± 10	0.250
≥75, n (%)	14 (16.9)	36 (10.1)	0.083
≥65, n (%)	38 (45.8)	143 (40.3)	0.359
Male gender, n (%)	56 (67.5)	278 (78.3)	0.037
BMI, kg/m^2	24.9 ± 3.4	25.0 ± 3.3	0.926
BMI >23 (Asia)	59 (71.1)	256 (72.1)	0.851
BMI ≥25 (WHO)	36 (43.4)	166 (46.8)	0.577
Cardiovascular risk factor, n (%)			
Hypertension	48 (57.8)	194 (54.6)	0.600
Diabetes	29 (34.9)	130 (36.6)	0.774
Dyslipidemia	16 (19.3)	59 (16.6)	0.563
Current Smoking	20 (24.1)	91 (25.6)	0.772
Prior CVD, n (%)			
Prior MI	9 (10.8)	55 (15.5)	0.280
Prior PCI	20 (24.1)	112 (31.5)	0.188
Prior CABG	1 (1.1)	6 (1.7)	>0.999
Clinical indication, n (%)			0.431
Stable angina	30 (36.1)	114 (32.1)	
Unstable angina	30 (36.1)	156 (43.9)	
Current MI	23 (27.7)	85 (23.9)	
CCS class †			0.020
I	0 (0)	3 (2.6)	
II	2 (6.7)	31 (27.2)	
III	16 (53.3)	59 (51.8)	
IV	12 (40.0)	21 (18.4)	
Syntax Score			0.353
Mean ± SD	21.4 ± 8.5	22.6 ± 11.3	
Median (95% CI)	20.0 (19.5–23.2)	20.5 (21.4–23.8)	
Syntax Score Class			0.430
Syntax Score ≤ 22	51 (61.4)	200 (56.3)	
Syntax Score 23–32	20 (24.1)	111 (31.3)	
Syntax Score ≥ 33	12 (14.5)	44 (12.4)	
LVEF, %	50.8 ± 12.0	50.4 ± 12.2	0.774
LVEF <50%, n (%)	30 (36.1)	134 (37.7)	0.786
LVEF <40%, n (%)	14 (16.9)	68 (19.2)	0.631
LVEF <35%, n (%)	7 (8.4)	38 (10.7)	0.540
Creatinine, mg/dl	1.08 ± 0.81	1.05 ± 0.70	0.704
Creatinine >2.0, n (%)	1 (1.2)	8 (2.3)	0.700
ACEF score	1.37 ± 0.55	1.34 ± 0.58	0.709
Post-PCI			
Post-PCI symptom			<0.001
Symptom-relief	34 (41.0)	242 (68.2)	
Symptom-residual	49 (59.0)	113 (31.8)	
Syntax Score			
Mean ± SD	21.4 ± 8.5	15.3 ± 11.1	<0.001
Median (95% CI)	20.0 (19.5–23.2)	12.5 (14.2–16.5)	
Syntax Score Class			<0.001
Syntax Score ≤ 22	51 (61.4)	292 (82.3)	
Syntax Score 23–32	20 (24.1)	36 (10.1)	
Syntax Score ≥ 33	12 (14.5)	27 (7.6)	
LVEF, %	48.3 ± 15.7	49.5 ± 12.8	0.850
LVEF <50%	15 (40.5)	74 (49.0)	0.355
LVEF <40%	11 (29.7)	46 (30.5)	0.931
LVEF <35%	10 (27.0)	30 (19.9)	0.340

Data are presented as mean ± SD, 95% (CI, confidence interval) or number (%).
BMI: body mass index, MI: myocardial infarction, CVD: cardiovascular disease. PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, LEVF: left ventricular ejection fraction, ACEF score: age creatinine, and ejection fraction score, CCS: Canadian cardiovascular society, †CCS class only display for the indication stable angina.

obvious bias to declare the successful PCI-CTO a winner, and failed to do so. Overall, the patients in our B-CTO Registry exhibited low mortality, non-fatal MI and stroke rates, despite the elevated risk ACEF score in both groups, which could reliably predict the clinical outcome in CTO patients treated with PCI [17]. Here, our findings do not confirm that an ACEF score was associated with hard clinical outcomes despite successful PCI. Therefore, it is still unclear which combination of clinical and angiographic characteristics in Korea is optimal for predicting successful PCI-CTO.

A meta-analysis of pooled CTO studies focused on in-hospital outcomes has been summarized lately, suggesting that failed PCI-CTO procedures were associated with higher rate of periprocedural complications (coronary perforation and cardiac tamponade), which were also seemed to be closely related to in-hospital mortality [18]. These data most definitely contradict with the index B-CTO results, and may be related to the differences in general health care, available facilities and equipment, so as experience of interventional cardiologists. There were very few periprocedural complications including single cases of coronary perforation, and cardiac tamponade, explaining lack of in-hospital cardiac death in our registry. Further study is warranted to validate the present results including the combined data from multi-centers in Eastern Asia with larger patient pool, or, better, specifically designed randomized outcome-driven trial.

5. Limitations

There are definite inherent limitations, which may influence the index results due to confounding factors. First, the data are driven from the open registry, although prospectively designed with the long follow-up. Because of high procedural success rate (80%), relatively small number of cases constituted the failure group. Second, differences in the interventional techniques, as well as clinical settings involved in PCI-CTO could vary over time since the registry was initiated as early as in 1999. Third, operator's technical skills and experience, which influenced on procedure success or not, as well as PCI complications should be also considered. Fourth, the anticoagulation protocol seems somewhat sub-therapeutic for retrograde approach for the US or Europe, but rather conventional in Korea. Finally, the detailed data about post-PCI medical treatment, especially in terms of dual antiplatelet therapy content and duration were not always available. Our Registry also suffers from the lack of formal structured follow-up, adjudication shortcomings, and unclear role of CTO in stroke development.

6. Conclusions

The risks of HMACE after PCI-CTO over long-term follow-up were minimal, and do not depend on the procedure success. This surprise finding should be confirmed in the adequately powered randomized trial. Obviously, yet unclear, compensatory mechanism to protect from failed CTO recanalization should be considered, and explored further somewhat challenging aggressive interventional approach.

Table 2
Clinical outcomes in B-CTO Registry.

	Failure (n = 83)	Success (n = 355)	Hazard Ratio (95% CI)	P value
Follow-up period, months				0.132
Mean ± SD	44.5 ± 46.2	49.9 ± 43.9	-	
Mean (95% CI)	44.5 (34.4–54.6)	49.9 (45.4–54.5)	-	
HMACE	5 (6.0)	11 (3.1)	0.47 (0.16–1.35)	0.162
Cardiac death	1 (1.2)	1 (0.3)	0.22 (0.01–3.50)	0.283
Non-fatal MI	3 (3.6)	4 (1.1)	0.27 (0.06–1.22)	0.089
Stroke	1 (1.2)	6 (1.7)	1.32 (0.16–10.99)	0.795

Data are presented as mean ± SD, 95% (CI) or number (%).
HMACE: hard major adverse clinical events (composite of cardiac death, non-fatal MI, and stroke).

Disclosures

The authors declare no conflicts of interest.

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