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Clinical outcomes after successful revascularization of long chronic total occlusions using amphilimus-eluting polymer-free stent: a single center experience

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Abstract. – OBJECTIVE: Chronic total occlusions (CTOs) are complex lesions that usually require stenting of long segments, and, therefore more prone to restenosis and/or thrombosis. Polymer-free stents to avoid chronic inflammatory response in the vessel wall are a potential solution to reduce target lesion revascularization. We, therefore, investigated the clinical outcomes following successful amphilimus-eluting polymer-free stent implantation in long CTOs.

PATIENTS AND METHODS: A total of 77 consecutive patients who underwent successful revascularization for long CTOs (lesion length ≥30 mm) using Cre8 stents were included. Baseline demographics, periprocedural characteristics, in-hospital events, and post-discharge long-term cardiovascular events were retrospectively screened for all patients.

RESULTS: The Japanese CTO score was 1.58 ± 0.96, and the lesion length was 54.0 ± 9.89 mm. All cases were technically successful (n = 77, 100%), while procedural success was obtained in 74 patients (96.1%). Periprocedural complications were contrast-induced nephropathy (n = 4, 5.2%), coronary perforation (n = 3, 3.8%), residual dissection (n = 1, 1.3%), and femoral artery pseudoaneurysm (n = 1, 1.3%). Three patients (3.9%) presented periprocedural myocardial infarction requiring repeat percutaneous coronary intervention. At 25.0 ± 15.8 months follow-up, major adverse cardiac and cerebrovascular events were observed in 14 patients (18.1%).

CONCLUSIONS: The Cre8 polymer-free drug-eluting stents seems safe and effective for percutaneous revascularization of long CTO lesions with a high success and low adverse event rate.

Key Words:
Angioplasty, Coronary artery disease, Drug-eluting stents.

Introduction

Percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) is one of the most complex procedures in interventional cardiology. In spite of the development of new techniques and equipment, procedural success rates in patients with CTO are still lower than those in non-CTO patients[1]. Studies[2-5] have shown that the risk of stent thrombosis and target lesion revascularization after PCI was significantly associated with the total stent length. From various registries, CTOs usually require long stents to be implanted, and thus these lesions have a greater risk of in-stent re-occlusion and thrombosis[6,7]. Previously, drug-eluting stents (DESs) have been shown[8] to reduce angiographic re-occlusion rates and the need for repeat revascularization compared to bare-metal stents (BMSs). However, the persistence of durable polymers in early-generation DESs has led to several problems, including local inflammatory reactions, delayed arterial healing, and neoatherosclerosis. Polymer-free DESs were developed for the complete elimination of these potential inflammatory stimuli of polymer coatings, possibly responsible for late stent thrombosis after stenting[9]. Among these, Cre8 stent (CID part of Alvimedica, S.P.A., Saluggia, Italy) utilizes sirolimus plus an organic acid, namely Amphilimus, that enhances bioavailability and drug distribution to the entire vessel wall. Recently, several clinical trials[10-12] have demonstrated the efficacy and the safety of Cre8 and have suggested that this DES may be useful in complex cases. The purpose of this study was to describe our center's experiences regarding the impact of Cre8 stent implantation on the long CTOs on clinical outcomes in real-world use.

Patients and Methods

Study Population

We first included 98 consecutive patients with a CTO who underwent PCI using cre8 stent(s), at our institution between January 2016 and May

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2021. Baseline demographics, angiographic and procedural characteristics, in-hospital events and post-discharge long-term cardiovascular (CV) events were retrospectively screened from our departmental database and hospital medical records for all patients. Patients needed a minimum of 6 months of complete follow-up to be included in the study. Follow-up was performed by means of phone interviews, review of the hospital records, or outpatient visits. Patients with symptom recurrence or with inducible ischemia were recommended to undergo angiographic evaluation. Eight patients with a CTO lesion failed to be opened, 4 patients with a follow-up duration of less than 6 months, and 9 patients with a short CTO lesion (angiographic lesion length < 30 mm) were excluded. The remaining 77 patients constitute our study cohort, and Figure 1 shows the flow chart of this study. Written informed consent was obtained from each subject involved. The Local Research Ethics Committee approved the study.

Definitions

A CTO itself was defined as a complete coronary obstruction with thrombolysis in myocardial infarction (TIMI) flow grade of zero and an estimated duration of ≥ 3 months. The duration of occlusion was estimated based on available clinical information related to the timing of the event that caused occlusion, for example, the first onset of anginal symptoms or history of myocardial infarction in the target vessel territory. Indications for CTO revascularization were exercise-induced angina resistant to pharmacological therapy or exercise-induced evidence of myocardial ischemia. Antegrade wire escalation (AWE) was defined as antegrade percutaneous coronary intervention (PCI) during which the guidewire crossed the lesion from 'true to true lumen'. Antegrade dissection re-entry (ADR) was defined as antegrade PCI during which a guidewire was intentionally introduced into the subintimal space proximal to the lesion, or re-entry into the distal lumen was attempted following intentional or inadvertent subintimal crossing. A procedure was defined as 'retrograde' if an attempt was made to cross the lesion through a collateral vessel or bypass graft supplying the target vessel distal to the lesion. Angiographic lesion length was measured during either antegrade or retrograde filling of the distal vessel, with simultaneous bilateral contrast injection if necessary. Lesion complexity was graded

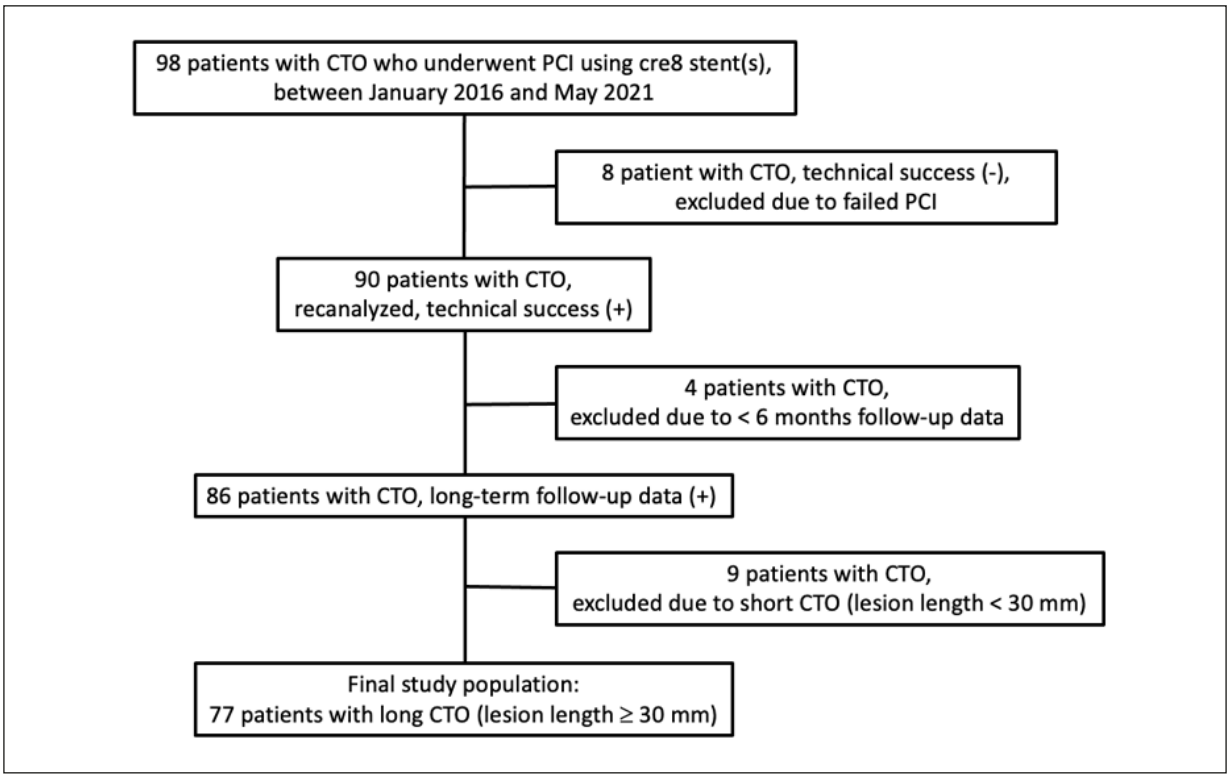

Figure 1. Flow chart of the study. CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

using the Japanese CTO (J-CTO) score[13]. Technical success was defined as restoration of TIMI III flow with stent implantation in the CTO segment and residual stenosis < 30%. Procedural success was defined as technical success plus the absence of in-hospital major adverse cardiac and cerebrovascular events (MACCE), including death, stroke/transient ischemic attack (TIA), periprocedural MI requiring PCI and periprocedural coronary artery bypass grafting (CABG). Long-term MACCE was defined as a composite of cardiac death, any MI, stroke/TIA and target lesion revascularization (TLR). All deaths were considered to be of cardiac origin unless a non-cardiac cause was established clinically or at autopsy. MI was defined as an elevation of cardiac troponin values ($> 5 \times 99^{th}$ percentile upper-reference limit) in patients with normal baseline values or as a rise in cardiac troponin values > 20% if the baseline values were elevated but stable or falling[14]. TLR was defined as target lesion re-intervention inside the implanted stent or within 5 mm proximally or distally by either PCI or CABG. Left ventricular ejection fraction was measured noninvasively by transthoracic echocardiography. Major bleeding was defined as bleeding causing a reduction in hemoglobin greater than 3 g/dl or bleeding requiring transfusion or surgical intervention. Contrast-induced nephropathy (CIN) was defined as an increase of ≥ 25% or ≥ 0.5 mg/dl in serum creatinine level at 48 hours after PCI.

Percutaneous Coronary nterventon Procedure

Arterial access was established through the radial and/or femoral arteries, and single or dual injection techniques were used for diagnostic angiography. If second arterial access was needed for dual injection in patients with femoral access, the radial approach was mostly preferred due to less access site bleeding complications, increased patient comfort, and faster postprocedural mobilization[15]. PCI procedures were performed with 6 or 7 Fr guiding catheters using standard techniques. Unfractionated heparin (10,000 IU bolus) was administered before the procedure to achieve an activated clotting time > 300 s. The initial antegrade approach, including antegrade wire escalation (AWE), parallel wire, and ADR techniques, was attempted. If the antegrade approach failed, we tried the retrograde approach using suitable collaterals available. Various available guidewires were used to cross the CTO lesion depending on lesion characteristics. In most cases, simple pre-dilation with a balloon was performed to obtain an adequate lumen diameter, which was necessary for the crossing of the unexpanded stent and its delivery system. If necessary, additional balloon dilations for lesion preparation and high-pressure post-dilations with non-compliant balloons were performed. All PCI procedures were performed using Cre8 DES (CID part of Alvimedica, S.P.A., Saluggia, Italy). Multiple stents were implanted if needed and were positioned using markers located at the proximal and distal edges.

Dual antiplatelet therapy was started before the index procedure, and all patients received aspirin (100 mg/day) and clopidogrel (300 to 600 mg loading dose, and 75 mg maintenance per day) for 12 months. Following a year, aspirin or clopidogrel was maintained life-long. Other medications, including beta blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and nitrates, were also continued to prescribe.

Statistical Analysis

The baseline clinical, angiographic, and procedural characteristics and in-hospital/long-term clinical outcomes were evaluated by descriptive statistics. Continuous variables were presented as mean ± standard deviation (SD) (or median, max, min, if needed), whereas categorical variables were expressed as count and percentages (%). MACCE-free survival and death-free survival were analyzed by the Kaplan-Meier method. Survival time was considered from the date of the CTO procedure to the end of the follow-up period or the occurrence of MACCE/death. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (Statistics for Windows IBM Corp., Armonk, NY, USA).

Results

Baseline Clinical Characteristics

The baseline clinical characteristics of the study population are shown in Table I. Most patients were men (71.4%, n = 55), and the mean age was 61.7 ± 11.1 years. One-third of the patients had a history of previous MI, and more than half had undergone PCI or CABG priorly. Multiple cardiovascular risk factors were observed in most patients, including hypertension (57.1%, n = 44), diabetes mellitus (40.3%, n = 31), smoking (76.6%, n = 59) and hyperlipidemia (74.0%, n =

Table I. Baseline clinical characteristics.

Variables	N = 77
Age (years)	61.7 ± 11.1
Gender (male) [n (%)]	55 (71.4%)
Hypertension [n (%)]	44 (57.1%)
Diabetes mellitus [n (%)]	31 (40.3%)
Current or previous smoking [n (%)]	59 (76.6%)
Hyperlipidemia [n (%)]	57 (74.0%)
Previous MI [n (%)]	21 (27.3%)
Prior PCI or CABG [n (%)]	44 (57.1%)
Prior stroke/TIA [n (%)]	5 (6.5%)
Chronic renal failure [n (%)]	7 (9.1%)
Normal LVEF (≥ 50%) [n (%)]	56 (72.7%)
Stable (vs. acute) presentation [n (%)]	45 (58.4%)

MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Grafting; TIA, Transient Ischemic Attack; LVEF, Left Ventricular Ejection Fraction.

57). Patients mostly presented a chronic, chest discomfort (58.4%, n = 45), while the others exhibited an acute, unstable presentation.

Angiographic and Procedural Characteristics

Angiographic and procedural characteristics of the study population are summarized in Table II. More than half of the patients had a multivessel disease (74%, n = 57) and only one had a left main disease (1.3%, n = 1). Nearly one out of five CTO segments were classified with blunt stump morphology. CTOs were mostly located in the right coronary artery (66.2%, n = 51) while in-stent CTOs were found in 11.7% of cases. According to the J-CTO score, 10.4% of lesions (n = 8) were scored as zero, 41.6% (n = 32) as 1, 29.9% (n = 23) as 2, 18.1% (n = 14) as 3 or higher. Dual injection technique (femoral + radial or femoral + femoral) was used in 80.5% (n = 62) and the only access used was femoral artery in the rest of the patients. Radial access was used in 66.2% (n = 51). AWE was the most frequently used technique (89.6%, n = 69) for crossing the lesions while ADR, parallel wire and retrograde techniques were performed in some cases (9.1%, n = 7; 19.4%, n = 15 and 1.3%, n = 1, respectively). Successful wire crossing was achieved with 'Pilot 200' (Abbott Vascular, St Paul, MN, USA) in 25.9% (n = 20), 'Fielder XT' (Asahi Intecc, Nagoya, Japan) in 18.2% (n = 14), 'Miracle' (Asahi Intecc, Nagoya, Japan) in 22.0% (n = 17), 'Conquest' (Asahi Intecc, Nagoya, Japan) in 33.7% (n = 26). The average lesion length and total stent length per target vessel were 54.0 ± 9.89 mm and 60.3 ± 12.7, respectively. A total of 122 Cre8 stents were implanted in 77 patients and mean number of stents per lesion was 1.58 ± 0.57. Mean contrast volume used was 295 ± 65 ml, with mean fluoroscopy time 65.8 ± 11.6 min, mean procedure time 90.1 ± 18.5 min and mean radiation dose 4,160 ± 1,320 mGy. Although all cases were technically successful, procedural success remains as 96.1% (n = 74).

Periprocedural and In-Hospital Outcomes

Periprocedural complications and in-hospital MACCEs are demonstrated in Table III. Four patients (5.2%) had contrast-induced nephropathy

Table II. Angiographic and procedural characteristics.

Variables	N = 77
Multivessel disease [n (%)]	57 (74.0%)
Left main disease [n (%)]	1 (1.3%)
Location of CTOs [n (%)]	
LAD	17 (22.1%)
LCx	9 (11.7%)
RCA	51 (66.2%)
In-stent CTOs	9 (11.7%)
Morphology of the CTO [n (%)]	
Blunt stump	14 (18.2%)
Calcification	31 (40.3%)
Tortuosity ≥ 45°	7 (9.1%)
Lesion length ≥ 20 mm	77 (100%)
Re – attempt	6 (7.8%)
J-CTO score	1.58 ± 0.96
Collateral circulation [n (%)]	
Antegrade	50 (64.9%)
Ipsilateral retrograde	7 (9.1%)
Contralateral retrograde	17 (22.0%)
Radial access [n (%)]	51 (66.2%)
Revascularization strategy [n (%)]	
AWE	69 (89.6%)
ADR	7 (9.1%)
Parallel wire	15 (19.4%)
Retrograde	1 (1.3%)
Crossing CTO wire used [n (%)]	
Soft guidewires (Fielder XT, pilot 200)	34 (44.1%)
Stiffer wires (Miracle, Conquest)	43 (55.8%)
Lesion length (mm)	54.0 ± 9.89
Total stent length (mm)	60.3 ± 12.7
Largest stent diameter (mm)	3.01 ± 0.38
Total number of stents	1.58 ± 0.57
Contrast volume (ml)	295 ± 65
Fluoroscopy time (min)	65.8 ± 11.6
Procedural time (min)	90.1 ± 18.5
Radiation dose (mGy)	4,160 ± 1,320
Technical success [n (%)]	77 (100%)
Procedural success [n (%)]	74 (96.1%)

AWE, Antegrade Wire Escalation; ADR, Antegrade dissection re-entry; CTO, Chronic Total Occlusion; LAD, Left Anterior Descending Artery; LCx, Left Circumflex Artery; RCA, Right coronary artery.

Table III. Periprocedural complications and in-hospital adverse events.

Variables	N = 77
Periprocedural complications [n (%)]	9 (11.6%)
Contrast induced nephropathy [n (%)]	4 (5.2%)
Cardiac tamponade [n (%)]	0 (0)
Perforation [n (%)]	3 (3.8%)
Residual dissection [n (%)]	1 (1.3%)
Vascular access complications [n (%)]	1 (1.3%)
Major bleeding [n (%)]	0 (0)
In-hospital MACCE [n (%)]	3 (3.8%)
Periprocedural MI and PCI [n (%)]	3 (3.8%)
Periprocedural CABG [n (%)]	0 (0)
In-hospital death [n (%)]	0 (0)
In-hospital stroke/TIA [n (%)]	0 (0)

CABG, Coronary Artery Bypass Grafting; MACCE, Major Adverse Cardiac and Cerebrovascular Event; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; TIA, Transient Ischemic Attack.

not requiring dialysis. Three patients (3.8%) had coronary perforation (all were Ellis 1 or 2) not related to cardiac tamponade. One patient (1.3%) had a residual coronary dissection not limiting distal flow and one (1.3%) also had an iatrogenic femoral artery pseudoaneurysm which was closed by percutaneous thrombin injection. Major bleeding was not seen in any patient. Although three patients (3.9%) presented periprocedural MI and need for repeat PCI, no patient showed periprocedural CABG, in-hospital death and in-hospital stroke/transient ischaemic attack (TIA).

Long-Term Clinical Outcomes

Follow-up was available for all patients with an average duration of 25.0 ± 15.8 (min: 6, max: 63, median: 21.0) months. Regarding long-term clinical outcomes (Table IV), the incidence of MACCE, including cardiac death (2.6%, n = 2), MI (5.2%, n = 4), stroke/TIA (2.6%, n = 2), and TLR (7.8%, n = 6) was 18.1% (n = 14) in total. During follow-up, some of these events overlapped in some patients and between patients (totally of fourteen events occurred in seven different follow-up durations). The Kaplan-Meier curves were generated to confirm these findings (Figure 2A-B).

Discussion

The main finding of this retrospective, multi-operator, single-center study was that Cre8 stent could safely be implanted with a low incidence of periprocedural complications, in-hospital adverse events and reasonable long-term MACCE rates in PCI procedures of patients with long CTO. These findings may be related to the stent's ultrathin design and polymer-free drug release system.

Due to the application of novel techniques and development of new generation stents in recent years, the success rate for PCI of CTOs seems to be higher[13,16]. Despite this, clinical and angiographic outcomes following CTO intervention remain worse than those following intervention for non-CTO disease[1,17]. The presence of CTO disease and lesion length are major predictors of major adverse cardiac events (MACEs) after stent implantation with DESs[18]. However, long-term clinical outcomes of intervention for long CTOs still need to be better understood.

The development of DESs has led to better rates of re-stenosis, re-occlusion, and adverse cardiac events for all kinds of coronary lesions[8]. Second-generation DESs utilize a cobalt-chromium or platinum stent platform and release antiproliferative agents *via* polymer coatings. Al-

Table IV. Clinical outcomes at long-term follow-up.

Variables	N = 77
Duration of follow-up (months)	25.0 ± 15.8 (max: 63, min: 6, median: 21.0)
MACCE [n (%)]	14 (18.1%)
Cardiac death [n (%)]	2 (2.6%)
Within 6 months [n (%)]	0 (0)
6 - 12 months [n (%)]	0 (0)
12 - 24 months [n (%)]	2 (2.6%)
> 24 months [n (%)]	0 (0)
Any MI [n (%)]	4 (5.2%)
Within 6 months [n (%)]	1 (1.3%)
6-12 months [n (%)]	1 (1.3%)
12-24 months [n (%)]	0 (0)
> 24 months [n (%)]	2 (2.6%)
Stroke/TIA [n (%)]	2 (2.6%)
Within 6 months [n (%)]	1 (1.3%)
6-12 months [n (%)]	1 (1.3%)
12-24 months [n (%)]	0 (0)
> 24 months [n (%)]	0 (0)
TLR [n (%)]	6 (7.8%)
Within 6 months [n (%)]	2 (2.6%)
6-12 months [n (%)]	1 (1.3%)
12-24 months [n (%)]	0 (0)
> 24 months [n (%)]	3 (3.9%)

MACCE, Major Adverse Cardiac and Cerebrovascular Event; MI, Myocardial Infarction; TIA, Transient Ischemic Attack; TLR, Target Lesion Revascularization.

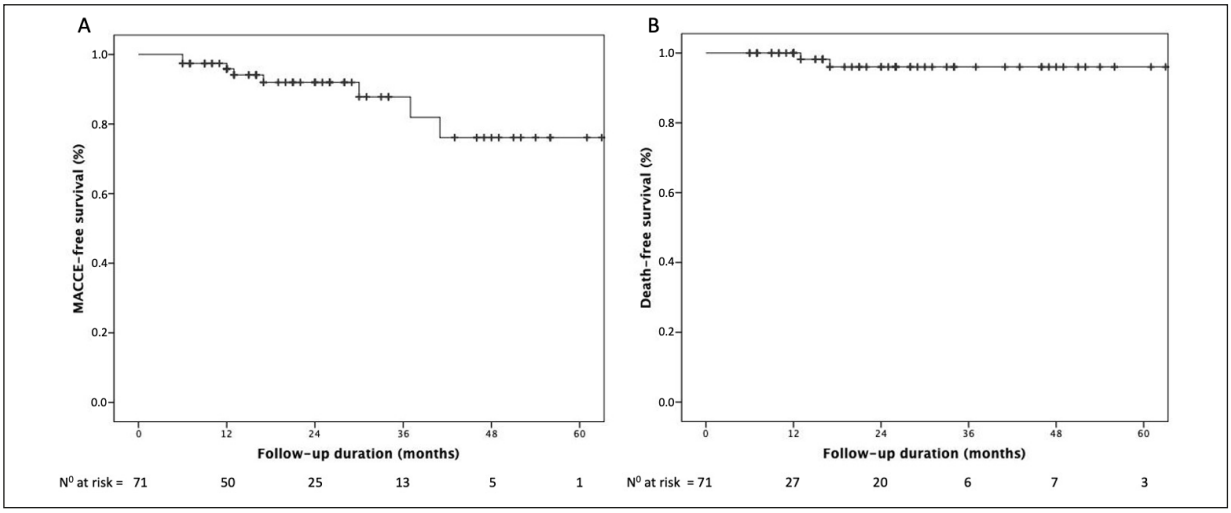

Figure 2. Kaplan-Meier survival curves for MACCE (**A**) and death (**B**). During follow-up, a total of fourteen events occurred in eight patients and seven different follow-up durations. The type and the timing of events for each patient were as follows: Patient 3: Stroke/TIA and Death (13th month); Patient 4: Death (17th month); Patient 14: TLR, MI, Stroke/TIA (6th month); Patient 17: TLR, MI (37th month); Patient 27: TLR (6th month); Patient 28: TLR, MI (12th month); Patient 48: TLR, MI (41st month); Patient 61: TLR (30th month). MACCE, Major adverse cardiac and cerebrovascular events; MI, Myocardial infarction; TIA, Transient ischemic attack; TLR, Target lesion revascularization.

though essential for effective drug release, the persistence of these durable polymers triggers chronic inflammation, delays endothelization and impairs arterial healing within the stented vascular segment, which results in a very late (> 12 months) stent thrombosis[19]. Contrary to second-generation DES, the Cre8 stent (third generation) is a cobalt-chromium, polymer-free DES with a strut thickness of 80 mm. Its proprietary drug release system utilizes a formulation of sirolimus plus an organic acid (Amphilimus) and consists of reservoirs on the stent's outer surface that control and direct drug release exclusively towards the vessel wall. The reservoir's design allows peak drug tissue concentration during the first post-implantation days and complete drug elution within 90 days[20].

Preclinical investigations on Cre8 DESs have shown[20] improved arterial healing with a lower degree of neointimal proliferation and inflammation compared with early generation durable-polymer sirolimus-eluting stent (Cypher Select Plus, Cordis, Johnson & Johnson, Warren, NJ, USA). Cre8 has been compared to the paclitaxel-eluting stent (Taxus Liberte, Boston Scientific, Natick, MA, USA) in a previous randomized study[10] demonstrating a significantly reduced in-stent late lumen loss (LLL) in comparison to Taxus at 6-months. Subgroup analysis has indicated no difference in LLL between patients with and without diabetes treated with Cre8, suggesting an advantage of this stent in diabetic population. A multicenter, randomized trial[21] (ReCre8) has shown non-inferiority in target-lesion failure as compared with permanent-polymer zotarolimus-eluting stent (Resolute Integrity, Medtronic Vascular, Santa Rosa, CA, USA), while Panoulas et al[22] have demonstrated non-inferior 1-year MACE rates, compared to those of new generation everolimus-eluting stents (Xience Prime, Abbott Vascular, Santa Clara, CA, USA). However, studies focusing on the safety and efficacy of the Cre8 stent implantation, in particular for complex lesions, are very limited. Maeremans et al[23] have recently indicated low rates of MACCE and target vessel failure up to 1 year in patients with Cre8 DES *vs.* non-polymer-free DES implantation for the percutaneous treatment of CTOs. In another study, Ahn et al[24] have investigated whether CTO lesion length can influence clinical outcomes following successful PCI of these lesions using DESs and have found a higher incidence of repeated PCI in patients with long CTO in comparison to those with short CTO.

The present study demonstrated our center's real-world experiences with periprocedural, in-hospital and long-term clinical outcomes in patients with technically successful Cre8 DES implantation, specifically to the long CTOs (>

30 mm). Lesion complexity was intermediate (mean J-CTO score = 1.58), and the procedural success rate was 96.1% (n = 74) in the current study. Only three (3.8%, n = 3) patients appeared with in-hospital MACCE, similar to the previous series[23,24]. In-hospital MACCE was driven only by periprocedural MI in our study (in-hospital mortality was zero) and might be caused by a variety of factors, including side branch closure, coronary artery dissection, and atheroembolism to distal branches. In other centers[25], using contemporary treatment, the incidence of perforation was reported to be approximately 5.5%. The rate was 3.8% (n = 3) in this study, and all perforations were classified as Ellis 1 (n = 2) or Ellis 2 (n = 1). The rate of contrast-induced nephropathy of this population (5.2%, none required dialysis) was also similar to the 5.8% rate reported by Demir et al[26]. Additionally, the mean volume of contrast, fluoroscopy time and radiation dose of our procedures were in accordance with previous series[23].

Previous observational studies[24,27,28] and a randomized controlled trial[29] investigating long-term MACE/MACCE rate after CTO intervention showed contradicting results. Jang et al[27] compared revascularization (by PCI or CABG) with optimal medical therapy alone in 738 CTO patients and indicated a 3.4% MACE rate at 42 months follow-up for the revascularization group. The Italian CTO Registry[28] also assessed one-year clinical outcomes of 1,777 patients with CTO, showing a 2.6% MACCE rate in patients treated with PCI in comparison to medical treatment and surgery (8.2% and 6.9%, $p < 0.001$). However, the current study demonstrated an 18.1% MACCE rate during a mean follow-up of 25 months, mostly driven by TLR (7.8%). This relatively higher MACCE rate may be attributed to the longer CTO lesion length, longer total stent length, and longer follow-up duration in our population compared to those previous observational studies[27,28]. Recently, the DECISION-CTO trial randomized 834 patients according to the CTO-PCI (n = 417) and no CTO-PCI (n=398) strategy. After a 4-year follow-up, the incidence of MACCE was 22.3% (*vs.* 22.4%) in CTO-PCI group, higher than our MACCE rates[29]. In another study, Ahn et al[24] compared two-year MACE rates between long and short CTOs irrespective of the stent type and revealed a 21.3% total MACE, 18.8% repeated PCI, 3.1% total mortality for patients with long CTOs, indicating higher event rates than those of our study, in spite of similar follow-up duration. This may be due to the ultrathin, polymer-free design and unique reservoir-based drug release system of the Cre8 stent, which was the only stent we used in our study.

Clinical Perspectives

To the best of our knowledge, this is the first observational study so far to investigate the long-term clinical outcomes of specifically long CTOs following successful percutaneous revascularization using polymer-free Cre8 DESs. Our report provides reassuring data in this regard, as we found a low incidence of periprocedural complications, in-hospital MACCE, and comparable MACCE rates for long-term follow-up with those of similarly designed studies after successful Cre8 stent implantation to CTO lesions more than 30 mm in length.

Study Limitations

Our study has some limitations. First, this was a single-center, retrospective, and observational study. All data were derived from a single hospital department, reflecting its current standard clinic practice. Second, the number of patients included was relatively small, because our study aimed to investigate a highly specific patient group (patients with long CTOs only and Cre8 DES implantation only). Therefore, our study may not have sufficient power to detect clinical outcomes. Third, CTO lesion length was mostly measured angiographically. Some other tests, such as intravascular ultrasound or optical coherence tomography, are necessary for more accurate measurement of CTO length. Fourth, the lack of a control group and/or short CTO group for comparison is another limitation of this study. Fifth, control coronary angiography during long-term follow-up was not routinely performed for all patients. Since well-developed collaterals and myocardial viability could influence ischemic symptoms, the need for repeated PCI might have been underestimated. Finally, a mean follow-up of 25 months may not be long enough to evaluate long-term safety and efficacy. Thus, a longer follow-up duration with a larger number of patients is needed for more definitive results.

Conclusions

The Cre8 polymer-free DESs appear to be safe and effective, with a positive impact on in-hospital and long-term clinical outcomes in

the treatment of patients with long CTOs. Large-scale, prospective and randomized clinical trials would be useful for further evaluating the clinical outcomes in long CTO lesions treated with amphilimus-eluting polymer-free stents.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Informed consent
Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials
The data presented in this study are available on request from the corresponding author.

Authors' Contribution
K.T.: Concept, Design, Data Collection, Writing, Critical Review; E.G.: Concept, Design, Data Collection, Analysis and/or interpretation, Writing; Z.D.: Data collection, Materials; T.G.: Data Collection, Materials; A.Ç.: Supervision, Critical Review; M.S.: Supervision, Critical Review.

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Ethics Approval
The study was approved by the Marmara University School of Medicine Ethics Committee (Date: 06.01.2023, Number: 09.2023.21).

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