Treatment of De Novo Chronic Total Occlusions with Drug-Coated Balloon-Only

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Abstract

The study aimed to investigate the impact of angiographic and clinical outcomes of the drug-coated balloon (DCB)-only treatment for de novo coronary chronic total occlusion (CTO).

One hundred one vessels with de novo CTO lesions dilated by balloon angioplasty with thrombolysis in myocardial infarction (TIMI) flow-grade 3 were assigned. Among them, we analyzed 93-vessel treated using DCB-only treatment. The primary endpoint was major adverse cardiac events (MACE), a composite of cardiac death, non-fatal myocardial infarction (MI), target vessel revascularization (TVR), and target vessel thrombosis. The secondary endpoint was late lumen loss (LLL) on follow-up coronary angiography.

All 84-patient were followed up clinically, and 67-vessel underwent scheduled coronary angiography after 6-month. There were no procedural complications, and three vessels required bailout-stenting. MACE occurred in 14 patients, including 2 cardiac deaths, 3 non-fatal MIs, and 11 TVRs. There was no target vessel thrombosis. The mean LLL was 0.03 ± 0.53mm. Binary restenosis occurred in 10 and re-occlusion in 2 vessels.

The results from a 2-year follow-up with DCB-only treatment are encouraging, with a low rate of hard endpoints and acceptable MACE rates. It may offer an alternative to the implantation of a drug-eluting stent if the CTO lesions have TIMI flow-grade 3 after pre-dilation.

Introduction

Chronic total occlusions (CTOs) comprise up to a fifth of the lesions detected by coronary angiography, and approximately half of them are treated with revascularization, while the other half are treated with medical therapy [1]. Percutaneous coronary intervention (PCI) for CTOs has rapidly evolved in recent years, and although there have been major improvements in equipment and techniques, CTO remains one of the biggest challenges for interventional cardiologists, especially as the risks of restenosis and stent thrombosis (ST) remain high. This aspect is most problematic for the vessel distal to the occlusion, which often enlarges after the restoration of antegrade flow; therefore, residual distal stenoses observed immediately after PCI of the CTO that do not affect antegrade flow may not require stenting [2].

There is much evidence that drug-coated balloon (DCB) treatment results in lower rates of restenosis and thrombosis, and better long-term outcomes when used for PCI of in-stent restenosis (ISR) compared to plain old balloon angioplasty or additional stenting with drug-eluting stents (DES) [3,4]. Considering the prevalence of CTOs and their high risk of restenosis and ST following PCI, it is necessary to investigate the safety and efficacy of DCB treatment in CTO PCI.

DCB-only studies for CTO are scarce; however, recent registry data suggest that it is a feasible and well-tolerated treatment, provided that the result from pre-dilation is good [5-8]. In the feasibility and safety assessment, the incidence of angiographic restenosis was 11.8% at a mean follow-up of 8 months. This

was not higher than prior results on CTO using either DES (14.2%) or bare-metal stents (36.6%) of 15 studies that included 3,193 patients [9]. Furthermore, positive late lumen gain was reportedly found in 67.6% of patients, which was attributed to an increase in DCB-treated vessel size [5]. Although registry data showed that DCB-only treatment for CTO is feasible, the clinical impact of DCB treatment on CTO PCI remains uncertain. Therefore, the aim of this study was to evaluate the impact in terms of angiographic and clinical outcomes of a DCB-only approach for de novo coronary CTO lesions.

Results

The study population consisted of 84 patients with de novo coronary CTO lesions (93 vessels) who had TIMI flow grade 3 and less than 70% of residual stenosis following pre-dilatation balloon angioplasty and were successfully treated with DCB without requiring stent implantation. All patients were followed up clinically up to a median of 720 days (interquartile range [IQR]: 406 to 1,268 days) after the index procedure; 72% of vessels underwent a 6-month scheduled angiographic follow-up (Fig. 1). Bailout stenting was needed in three patients (3 vessels) after DCB treatment (due to TIMI flow grade 1 and type E dissection in 2 and 1 vessels, respectively; all these lesions were treated with new-generation DES). Overall, the angiographic success rate was 95.7%, and there were no in-hospital adverse cardiac events.

Baseline clinical characteristics of included subjects are shown in Table 1. The mean age was 56 years, and most patients were male (85.7%), with just over a third having diabetes mellitus. The mean left ventricular ejection fraction was 50.4 ± 12.9% (ejection fraction ≤ 35% in 9.5% of patients). Clinical presentations were chronic stable angina (61.9%) and acute coronary syndrome (38.1%).

Table 1
Baseline patient characteristics

	n = 84 patients
Age,years	56.1 ± 9.9
Male	72 (85.7)
Hypertension	49 (58.3)
Hypercholesterolemia	40 (47.6)
Diabetes	32 (38.1)
Current smoker	16 (19.0)
Previous myocardial infarction	21 (25.0)
Previous percutaneous intervention	21 (25.0)
Previous coronary artery bypass grafting	0
Previous stroke	6 (7.1)
Family history of coronary artery disease	26 (31.0)
Hemodialysis	1 (1.2)
Ejection fraction, %	50.4 ± 12.9
Clinical presentation	
Chronic stable angina	52 (61.9)
Acute coronary syndrome	32 (38.1)
CCS classification	
0 to 2	73 (86.9)
3 or 4	11 (13.1)
Medication at discharge	
Aspirin	83 (98.8)
P2Y12 inhibitor	84 (100.0)
Statin	79 (94.0)
Vasodilator	45 (53.6)

Values are mean ± SD or number (percentage). CCS = canadian cardiovascular society grading of angina pectoris

Table 2 summarizes angiographic and procedural data. Most patients were treated via radial access, and the median SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score was 21.5 (IQR: 15.5 to 28.0) (53.8% <23 points, 28% 23–32 points, and 18.3% >32 points). The mean of the J-CTO score was 1.4 ± 0.6mm (category of difficulty from intermediate to difficult group). The left anterior descending artery was treated in 48.4% of cases, and a scoring balloon was used to treat a fifth of vessels. The mean pre-dilation balloon diameter was 2.4 ± 0.5mm, and the DCB diameter was 2.7 ± 0.4mm. SeQuent® Please DCB was used in the majority of cases (80.6%). The mean number of used DCBs was 1.5 ± 0.6, and the DCB to reference vessel ratio was 1.0 ± 0.2. The mean DCB length was 42.3 ± 17.1mm. The mean inflation time was 72.0 ± 29.7 s. After DCB treatment, 73.1% of vessels had dissections (type A, 23.7%; type B, 43.0%; type C, 4.3%; type D, 1.1%; and type E, 1.1%). Chronic stable angina (66.2%) and left anterior descending artery (51.5%) were more frequent in the dissection group. One type E dissection received bailout stenting with a DES. Almost all dissections disappeared (93.6%) at the follow-up coronary angiography. Representative images of the impact of DCB treatment on de novo CTO are shown in Central illustration B and Fig. 2.

Table 2
Angiographic and procedural characteristics

	n = 93 vessels
Radial artery access	82 (88.2)
Syntax score, median (IQR)	21.5 (15.5–28.0)
Number of diseased vessels	1.8 ± 0.8
Targeted vessel	
Left anterior descending artery	45 (48.4)
Left circumflex artery	24 (25.8)
Right coronary artery	24 (25.8)
Scoring balloon used	19 (20.4)
Pre-dilation balloon diameter, mm	2.4 ± 0.5
Pre-dilation balloon maximal pressure, atm	12.7 ± 4.2
DCB type	
SeQuent please family	75 (80.6)
IN.PACT Falcon	18 (19.4)
Number of DCB used	1.5 ± 0.6
DCB diameter, mm	2.7 ± 0.4
DCB to reference vessel ratio	1.0 ± 0.2
DCB length, mm	42.3 ± 17.1
DCB maximal pressure, atm	9.4 ± 2.7
DCB inflation time, second	72.0 ± 29.7
Dissection type after DCB	
None	25 (26.9)
A	22 (23.7)
B	40 (43.0)
C	4 (4.3)
D	1 (1.1)

Values are mean ± SD or number (percentage). IQR = interquartile range, DCB = drug-coated balloon

	n = 93 vessels
E	1 (1.1)
Bail-out stenting	3 (3.2)
Dissection at follow-up	N = 67
None	64 (95.5)
A	0
B	3 (4.5)
C	0
Values are mean ± SD or number (percentage). IQR = interquartile range, DCB = drug-coated balloon	

Angiographic outcomes

Sixty-one (72.6%) patients returned for scheduled follow-up angiography at a median of 186 days (IQR: 134 to 291 days) after their index procedure, ensuring that serial QCA data were available for 67 vessels. Angiographic outcomes are presented in Table 3, and representative cases of each coronary artery are shown in Fig. 2. Due to the nature of the CTO, the baseline QCA data required to calculate the LLL were only available after DCB treatment. The mean reference vessel diameter (RVD) after DCB treatment was 2.3 ± 0.5mm, while the mean residual diameter stenosis was 30.6 ± 9.3%. The acute lumen gain was 1.6 ± 0.4mm. Binary restenosis occurred in 10 (14.9%) treated vessels, and among them, 2 (3.0%) lesions were totally re-occluded at follow-up angiography. The secondary endpoint of LLL was 0.03 ± 0.53mm, with LLL values in 37 (55.2%) lesions below 0 due to an increase in vessel size.

Table 3
Quantitative coronary angiography and late luminal loss

	n = 93 vessels
Post-DCB treatment	
Reference vessel diameter, mm	2.3 ± 0.5
Lesion length, mm	42.4 ± 17.0
Minimal lumen diameter, mm	1.6 ± 0.4
Diameter stenosis, %	30.6 ± 9.3
Acute lumen gain, mm	1.6 ± 0.4
Follow-up	n = 67 vessels
Reference vessel diameter, mm	2.5 ± 0.7
Lesion length, mm	43.7 ± 16.8
Minimal lumen diameter, mm	1.6 ± 0.6
Diameter stenosis, %	37.8 ± 17.3
Late lumen loss, mm	0.03 ± 0.53
Binary restenosis	10/67 (14.9)
Scheduled angiography follow-up duration, day, median (IQR)	186 (134–291)
Values are mean ± SD. DCB = drug-coated balloon, IQR = interquartile range	

There was no significant change in minimum lumen diameter (MLD) between the index procedure and follow-up angiography (Table 3 and Supplementary Table 1, post-DCB vs. follow-up, 1.6 ± 0.4mm vs. 1.6 ± 0.6mm; p = 0.675); however, RVD was significantly larger at follow-up than post-DCB (post-DCB vs. follow-up, 2.3 ± 0.5mm vs. 2.5 ± 0.7mm; p = 0.033), hence the diameter stenosis rose significantly with follow-up (post-DCB vs. follow-up, 31.5 ± 9.0% vs. 37.8 ± 17.3%; p = 0.005).

Clinical outcomes

Table 4 summarizes procedural complications and clinical outcomes. There were no procedural complications, such as perforation, pericardiocentesis, emergency bypass surgery, or stroke, in this registry. The primary endpoint of MACE occurred in 14 (16.7%) patients, including cardiac death (2.4%), non-fatal MI (3.6%), and TVR (13.1%); there was no target vessel thrombosis (0%). Among the two cardiac deaths, one patient passed away 4-month after follow-up due to decompensated heart failure secondary to pneumonia and the other patient passed away out-of-hospital 9-month after follow-up; cause of death was determined as a heart attack. Of the TVR, six patients were treated with DES, 1 underwent coronary

artery bypass graft surgery, and 3 were treated with repeat DCB. The rate of non-TVR was 10.7%, with no stroke.

Table 4
Procedural complications and clinical outcomes

	n = 84 patients
Procedural complication	
Perforation	0
Pericardiocentesis	0
Emergency coronary artery bypass grafting	0
Stroke	0
Clinical outcomes	
Major adverse cardiac events	14 (16.7)
All death	2 (2.4)
Cardiac death	2 (2.4)
Non-fatal myocardial infarction	3 (3.6)
Target lesion revascularization	11 (13.1)
Target vessel revascularization	11 (13.1)
New vessel revascularization	9 (10.7)
Target vessel thrombosis	0
Stroke	2 (2.4)
Clinical follow-up duration, day, median (IQR)	720 (406–1268)
Values are mean ± SD or number (percentage). IQR = interquartile range	

Discussion

In the present study, we investigated the impact in terms of angiographic and clinical outcomes of DCB-only treatment for de novo coronary CTO lesions. The main findings were as follows: first, after successful balloon angioplasty of de novo CTO lesions, the DCB-only treatment is feasible and effective; second, the rate of MACE, the primary endpoint, was 16.7%, and was driven primarily by TVR with no target vessel thrombosis during a median follow-up of 720 days; third, LLL, the secondary endpoint, was minimal (0.03 ± 0.53mm), confirming the efficacy of DCB in inhibiting neointimal hyperplasia.

Although DES has significantly reduced the incidence of restenosis and clinical events compared with bare-metal stents, there are still risks associated with their use, such as pro-inflammatory effect that cause neoatherosclerosis, and ST due to delayed neointimal coverage [10,11]. With first-generation DES, ST accrued at a rate of 0.6% per year [12], while rates fell to 0.3% per year with second-generation DES. This risk persists for at least 5 years after stent insertion [13]. In a recent large-scale, individual patient-level pooled study (n = 25,032), very-late ST occurred between 1 and 5 years after PCI at a rate of 0.4% per year with all stent types, with no plateau evident [14]. In contrast to DES, DCBs can reduce this risk, while eluting drugs for a short period of time can effectively prevent neointimal hyperplasia in the absence of foreign substances, as shown in several DCB experiments with long-term follow-up [6,15]. In the SCAAR registry, the rate of target lesion thrombosis in de novo lesions in small coronary vessels undergoing PCI was 0.6% at 6 months, with no events between 6 months and final follow-up at 3 years [15]. In the BASKET-SMALL 2 trial, which was a multicenter, open-label, randomized non-inferiority trial for small native coronary artery disease (n = 758), probable or definite ST was lower with DCBs (0.8% DCB vs. 1.1% DES; hazard ratio [HR] 0.73 [0.16–3.26]) [6]. Recently, they showed MACE for 3 years, but it was not different compared to DES that was 15% in both the DCB and DES groups (HR 0.99, 95% CI 0.68–1.45; p = 0.95). The rates of probable or definite stent thrombosis (Kaplan-Meier estimate 1% vs 2%; HR 0.33, 95% CI 0.07–1.64; p = 0.18) and major bleeding (Kaplan-Meier estimate 2% vs 4%, HR 0.43, 95% CI 0.17–1.13; p = 0.088) were numerically lower in DCB versus DES.

In this study of de novo CTO lesions treated with DCB-only treatment, there were no cases of target vessel thrombosis during a median follow-up of 720 days despite similar lesion severity compared to previous CTO studies [14,16]. In the DECISION-CTO trial [17], the SYNTAX score was 20.8 ± 9.2, and the mean stent length was 41.1 ± 25.9mm. In comparison, the median SYNTAX score in our study was 21.5 (15.5–28.0), and lesion length was 42.3 ± 17.1mm, which generally does not differ from the CTO lesions that were treated with stents in previous studies [18,19]. Nevertheless, MACE results were similar to those detected by the DECISION-CTO trial, which used second-generation DES in 82.6% of patients. In the DECISION-CTO trial, the rates of cardiac death, MI, and TVR were 1.9%, 11.3%, and 7.9%, respectively; our study showed comparable event rates (2.4%, 3.6%, and 13.1%, respectively). In the DECISION-CTO trial, the rate of definite ST was 0.2% during a median follow-up of 4 years, while the rate of definite or probable ST was 0.4% in the EURO-CTO trial at 12 months follow-up [18].

The high risk of restenosis and ST in patients with CTO remains a challenging problem. One of the mechanisms for these clinical events is that stents in newly opened CTOs are commonly undersized because the vessel does not grow immediately after recanalization [20]. Vessels distal to a CTO are narrow because of blood flow absence for a long time. After balloon angioplasty, antegrade flow increases, and vessels become more expansive, but this may take several weeks or months. Therefore, immediately after balloon angioplasty of a CTO, it is easy to underestimate the actual vessel size, thus increasing the risk of stent undersizing and subsequent risks of restenosis, late stent malapposition, and ST. Moreover, the metallic cage can inhibit positive remodeling, leaving a small luminal size after vessel recovery. However, after treatment with a DCB, vessels may return to their original size over time, without fixing the size of

the vessel with a foreign body such as a stent, which is one of the most appealing and important advantages of using DCB in the treatment of CTO lesions. Only a few studies have investigated the impact of DCB-only treatment for de novo CTO lesions. According to a recent study, DCBs were successfully used for two totally occluded lesions in a patient with acute coronary syndrome. Three months later, follow-up angiography confirmed adequate patency of the DCB-treated lesions, with no symptoms until 13 months. Recently, Kleber et al. showed that DCB is a feasible and well-tolerated treatment that provided promising results from pre-dilation [5]. They showed that the positive late lumen gain in 67.6% of patients was due to increased vessel size following DCB treatment. This is comparable to our data, which confirmed positive late lumen gain in 55.2% of patients.

Strengths and limitations

The most compelling advantage of our study is that DCB treatment without stenting might be a safe and effective treatment method for de novo CTO if the result after pre-dilation is good with TIMI flow grade 3.

However, our study has several limitations. First, the population is limited and comes from two expert centers in this type of PCI. Thus, it may not be reproducible everywhere without an adequate learning curve. Second, this study did not target all-comers, but consisted only of patients who were successfully reperfused by pre-dilation and received DCB treatment. Therefore, attention should be paid to interpreting the results of this study. Prospective and randomized large-scale studies are needed to clarify the efficacy of DCB treatment for de novo CTO lesions compared to DES implantation.

Conclusions

The results from a 2 years follow-up with DCB-only treatment are encouraging, with a low rate of hard endpoints and acceptable MACE rates. It may offer an alternative to the implantation of a drug-eluting stent if the CTO lesions have TIMI flow grade 3 after pre-dilation.

Methods

Patient population

This retrospective observational study was conducted at two centers (Queen Elizabeth Hospital II and Ulsan Medical Center) experienced in treating patients with de novo CTOs with DCB (SeQuent® Please; B. Bruan Melsungen AG, Berlin, Germany or IN.PACT™ Admiral™; Medtronic, Minneapolis, USA) treatment (Impact of Drug-coated Balloon Treatment in de Novo Coronary Lesion; NCT04619277). One hundred one vessels (92 patients who have consented) with de novo CTO lesions dilated by balloon angioplasty with thrombolysis in myocardial infarction (TIMI) flow grade 3 were assigned. Among them all patients with successful PCI (defined as thrombolysis in myocardial infarction [TIMI] flow grade 3 and residual stenosis < 70%) for de novo CTO lesions performed using only DCB were eligible for inclusion. For each lesion, all applicable score values were summed to obtain a total difficulty score for that lesion (J-CTO

score) [21]. Patients with DCB treatment for a CTO due to occlusive in-stent restenosis, additional stents placed in the target vessel during the index procedure, or unstable hemodynamic conditions at presentation were excluded. The study protocol was approved by the institutional review board or ethics committee at each participating center (Queen Elizabeth Hospital II and Ulsan Medical Center), and all patients provided written informed consent. The study protocol was performed in accordance with the Declaration of Helsinki.

Procedure

All interventions were performed using the antegrade approach for recanalization. The intervention was performed according to the International DCB Consensus and the Asia-Pacific Consensus on DCB PCI [22,23]. Specifically, an optimal sized pre-dilation balloon, including a scoring balloon, was mandatory used at the recommended balloon-to-vessel ratio of 0.8–1.0. After pre-dilation balloon angioplasty, stenting was deferred even in the presence of Type A to E dissections (National Heart, Lung, and Blood Institute classification system for intimal tears by the Coronary Angioplasty Registry) [24], provided there was TIMI flow grade 3. In cases of flow-limiting dissection after pre-dilation (TIMI flow grade < 3), ≥ 70% of residual stenosis, and left main disease, PCI with stent insertion was recommended without using a DCB. The DCB was inflated for at least 60s with its nominal pressure. After DCB use, a final assessment was undertaken after at least 5 min with intracoronary vasodilator injection, such as nitroglycerin, to catch early vessel closure. In this event, bailout stenting was considered. A bailout glycoprotein IIb/IIIa receptor inhibitor strategy was allowed in cases of high thrombus burden. The duration of the prescribed dual antiplatelet therapy was left to the discretion of the attending doctors.

Definitions

CTOs are completely occluded coronary arteries without antegrade coronary flow with a duration > 3 months [25]. Angiographic success was defined as a final residual stenosis < 50% by quantitative coronary angiography (QCA), with TIMI flow grade 3 after DCB treatment. Procedural success was defined as angiographic success without the occurrence of in-hospital adverse cardiac events (defined as any occurrence of cardiac death, non-fatal MI, target vessel revascularization [TVR] or target vessel thrombosis). Binary restenosis was defined as a stenosis of at least 50% of the luminal diameter at the angiographic follow-up.

Endpoints

The primary endpoint was cumulative major adverse cardiac events (MACE), a composite of cardiac death, non-fatal myocardial infarction (MI), TVR, and target vessel thrombosis during follow-up. The secondary endpoint was late lumen loss (LLL) at the 6-month scheduled follow-up angiography.

Statistical analysis

Analyses were performed on a per-patient basis for clinical characteristics and primary outcome (and its individual components) and on a per-vessel basis for vessel-related parameters and vessel-level clinical outcomes. Categorical variables are presented as number with relative frequency (percentage) and continuous variables as mean with standard deviation or medians with first and third quartiles according to their distributions determined by the Kolmogorov-Smirnov test. For the demographic information, continuous data were summarized by descriptive statistics (number of subjects, mean, standard deviation) and categorical data by frequency and fraction. For the comparison between two the groups were evaluated using the independent two-sample t-test or Wilcoxon rank-sum test. If necessary, a Chi-square test or Fisher's exact test was performed to compare the two groups. All statistical analyses were performed at a two-sided significance level of 0.05, using SPSS version 21.0 (IBM Corp., Armonk, NY, USA), NCSS (NCSS LLC, East Kaysville, UT, USA), and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Abbreviations

DCB Drug-coated balloon

DES Drug-eluting stent

CTO Chronic total occlusion

MACE Major adverse cardiac events

TLR Target lesion revascularization

TVR Target vessel revascularization

Declarations

Funding

None

Competing interests

The authors have no conflicts of interest to declare.

Authorship contributions

Contributors ES and H.B.L contributed substantially to the design of the present study. E.J.J and E.S provided the first draft of the manuscript. E.J.J, ET, and YB performed the data analyses and the statistical analyses. All co-authors participated in the interpretation of data and critically revised the manuscript. The authors confirm that the manuscript has been blinded to follow the double-blind peer

review model. All authors have approved the final version of the manuscript. E.S and H.B.L. had full access to the database and take responsibility for the integrity and of the data and the data analyses.

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References

1. Azzalini, L. *et al.* Epidemiology, Management Strategies, and Outcomes of Patients With Chronic Total Coronary Occlusion. *Am J Cardiol* **118**, 1128-1135 (2016).
2. Gomez-Lara, J. *et al.* Lumen enlargement of the coronary segments located distal to chronic total occlusions successfully treated with drug-eluting stents at follow-up. *EuroIntervention* **9**, 1181-1188 (2014).
3. Scheller, B. *et al.* Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* **355**, 2113-2124 (2006).
4. Unverdorben, M. *et al.* Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. *EuroIntervention* **11**, 926-934 (2015).
5. Koln, P. J. *et al.* Treatment of chronic total occlusions in native coronary arteries by drug-coated balloons without stenting - A feasibility and safety study. *Int J Cardiol* **225**, 262-267 (2016).
6. Jeger, R. V. *et al.* Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. *Lancet* **396**, 1504-1510 (2020).
7. Venetsanos, D. *et al.* Long-term efficacy of drug coated balloons compared with new generation drug-eluting stents for the treatment of de novo coronary artery lesions. *Catheter Cardiovasc Interv* **92**, E317-E326 (2018).
8. Yuan, S. L., Kim, M. H., Garg, S. & Shin, E. S. A case of drug-coated balloon treatment for two total occluded lesions in a patient with acute coronary syndrome. *Cardiol J* **27**, 320-321 (2020).
9. Yang, S. *et al.* Efficacy of drug-eluting stent for chronic total coronary occlusions at different follow-up duration: a systematic review and meta-analysis. *Eur Rev for Med and Pharmacol Scien* **19**, 1101-1116 (2015).
10. Joner, M. *et al.* Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* **48**, 193-202 (2006).
11. Nakazawa, G., Vorpahl, M., Finn, A. V., Narula, J. & Virmani, R. (American College of Cardiology Foundation Washington, DC, 2009).
12. Daemen, J. *et al.* Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* **369**, 667-678 (2007).

13. Von Birgelen, C. *et al.* Five-year outcome after implantation of zotarolimus-and everolimus-eluting stents in randomized trial participants and nonenrolled eligible patients: a secondary analysis of a randomized clinical trial. *JAMA Cardiol* **2**, 268-276 (2017).
14. Madhavan, M. V. *et al.* Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention. *J Am Coll Cardiol* **75**, 590-604 (2020).
15. Silverio, A. *et al.* Percutaneous Treatment and Outcomes of Small Coronary Vessels: A SCAAR Report. *JACC Cardiovasc Interv* **13**, 793-804 (2020).
16. Moreno, R. *et al.* Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions: results from the chronic coronary occlusion treated by everolimus-eluting stent randomized trial. *Circ Cardiovasc Interv* **6**, 21-28 (2013).
17. Lee, S. W. *et al.* Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. *Circulation* **139**, 1674-1683 (2019).
18. Werner, G. S. *et al.* A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* **39**, 2484-2493 (2018).
19. Lee, P. H. *et al.* Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. *JACC Cardiovasc Interv* **9**, 530-538 (2016).
20. Shin, E. S. *et al.* Provisional drug-coated balloon treatment guided by physiology on de novo coronary lesion. *Cardiol J* (2020).
21. Morino, Y. *et al.* Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *J Am Coll Cardiol* **4**, 213-221 (2011).
22. Her, A. Y. *et al.* Drug-coated balloon treatment in coronary artery disease: Recommendations from an Asia-Pacific Consensus Group. *Cardiol J* **28**, 136-149 (2021).
23. Jeger, R. V. *et al.* Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. *JACC Cardiovasc Interv* **13**, 1391-1402 (2020).
24. Shimony, A., Joseph, L., Mottillo, S. & Eisenberg, M. J. Coronary artery perforation during percutaneous coronary intervention: a systematic review and meta-analysis. *Can J Cardiol* **27**, 843-850 (2011).
25. Tajti, P. *et al.* Update in the Percutaneous Management of Coronary Chronic Total Occlusions. *JACC Cardiovasc Interv* **11**, 615-625 (2018).

Figures

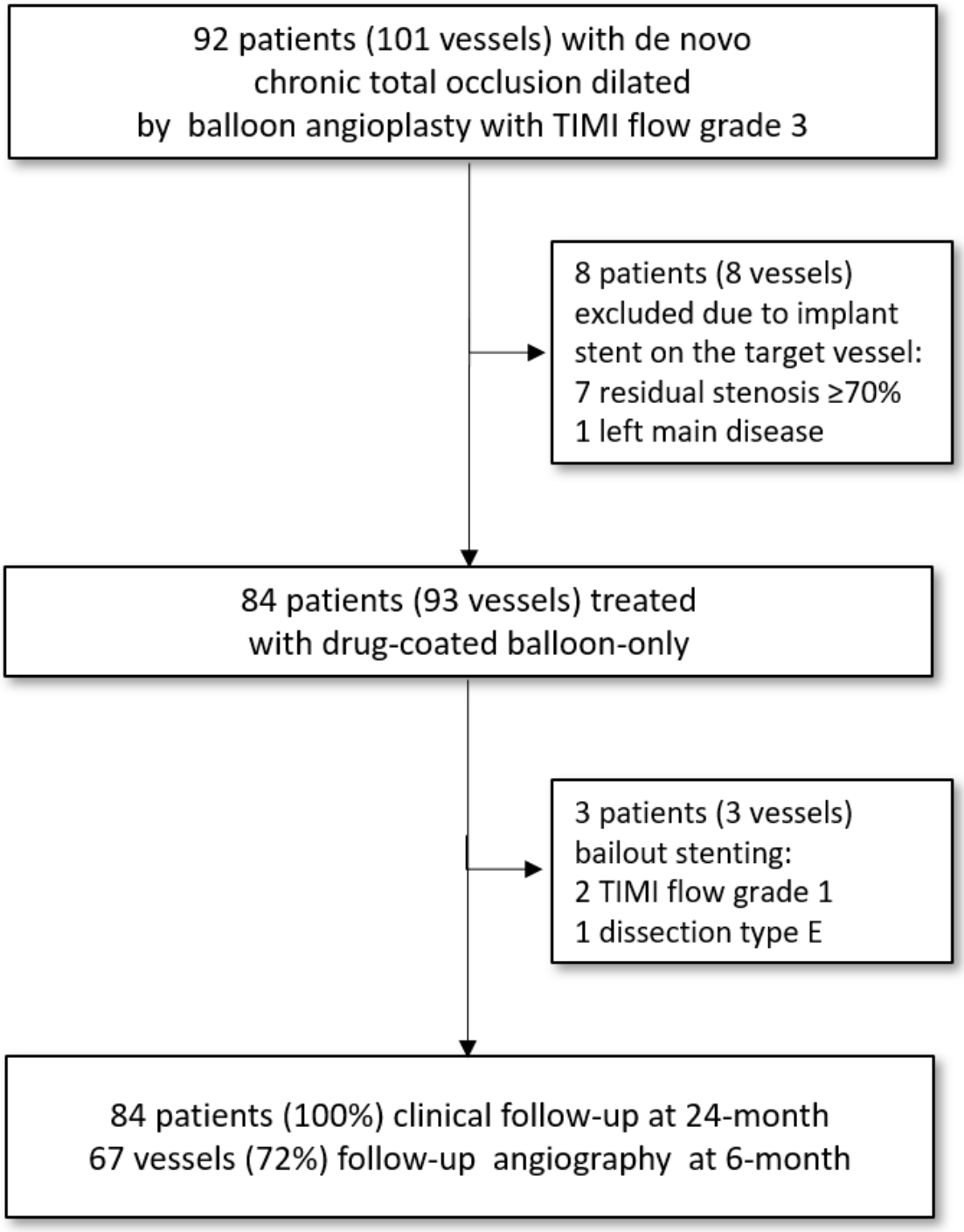

Figure 1

Flow chart of the study. TIMI = thrombolysis in myocardial infarction

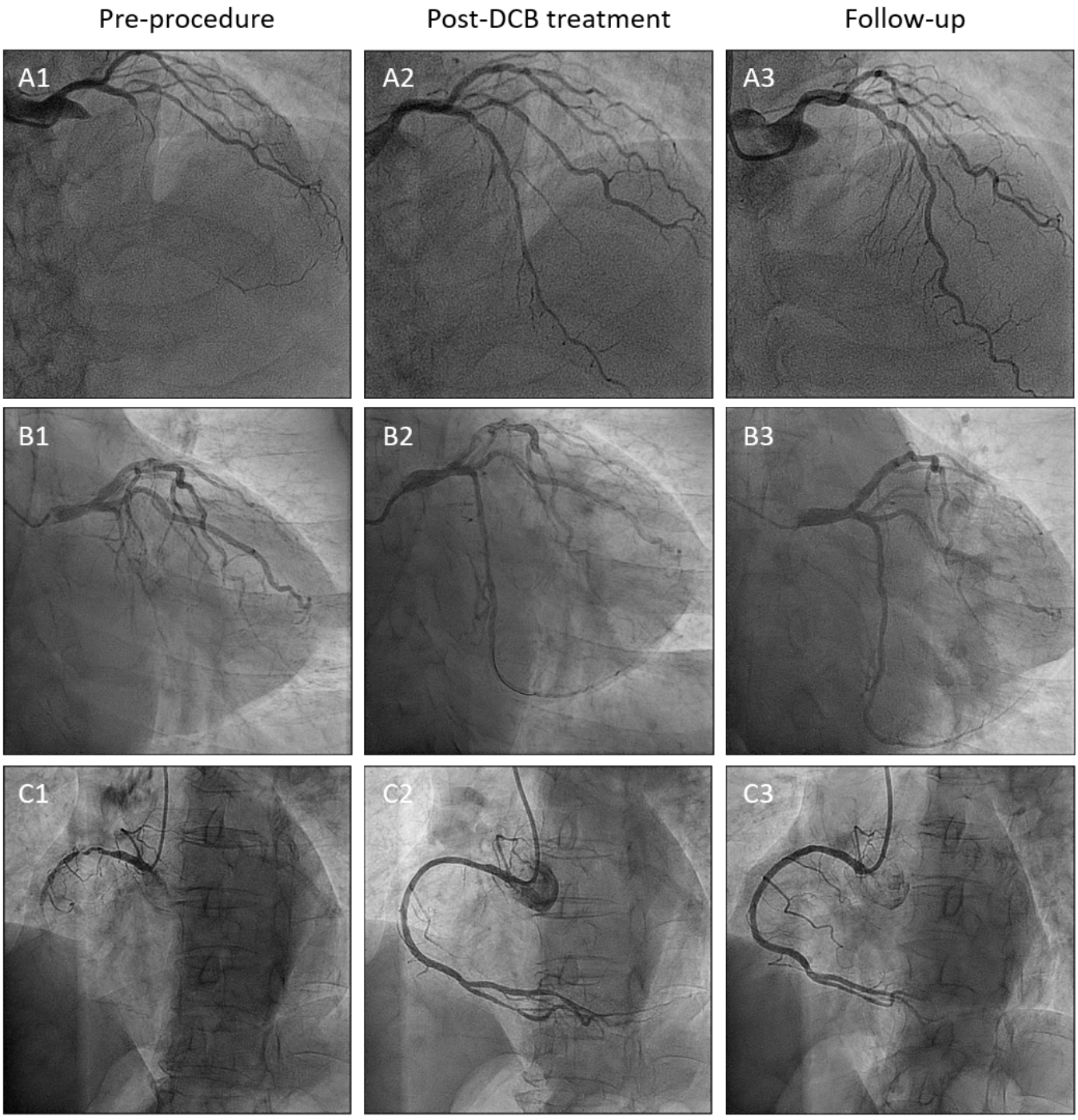

Figure 2

Representative CTO cases. A. Left anterior descending artery lesion; B. Left circumflex artery lesion; C. Right coronary artery lesion. Number 1: Pre-procedure; Number 2: Post-DCB treatment; Number 3: Follow-up

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx