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Drug-Coated Balloon-Based Treatment of Unprotected *de Novo* Left Main Coronary Artery Disease

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Research Article

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ABSTRACT

Objective: The aim of this study was to evaluate the safety and efficacy of DCB-based treatment for unprotected Left Main (LM) coronary artery disease.

Method: This retrospective registry study comprised a total of 42 consecutive patients diagnosed with unprotected *de novo* LM disease and stable hemodynamic conditions. A successful pre-balloon angioplasty was defined as achieving visual residual stenosis ≤ 30% without flow-limiting dissection and was followed by DCB (Drug Coated Balloon) treatment. Patients who did not meet these criteria were treated with a Drug-Eluting Stent (DES).

Results: Among the cohort of 42 patients, 23 individuals received DCB-only treatment, while based on the results of pre-balloon angioplasty, 19 patients were treated DES. Notably, no instances of bailout stenting or emergency coronary bypass surgery were observed following DCB treatment. Additionally, there were no reported cases of mortality or myocardial infarction within the DCB-only group during both hospitalization and the one-year follow-up period. Two patients (8.7%) experienced target lesion revascularization, all of whom presented with stable angina. A luminal increase was observed in 46.7% of cases, and the mean late lumen loss in the DCB-only treatment group was measured as 0.07 ± 0.45 mm.

Conclusion: DCB-based treatment of unprotected LM disease may be a safe and effective alternative to DES in carefully selected patients who have achieved successful predilation results. (Impact of Drug-Coated

Balloon Treatment in *de Novo* Coronary Lesion; NCT04619277).

Keywords: Left main coronary artery disease; Drug-coated balloon; *de novo*; Outcomes; Percutaneous coronary intervention

INTRODUCTION

The advancements in percutaneous intervention techniques and stent technology have expanded the role of Percutaneous Coronary Intervention (PCI) in the management of Left Main (LM) disease. According to the current guidelines of the European Society of Cardiology, LM lesions with intermediate SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score are classified as a class IIa indication for PCI with a level of evidence [1]. However, despite the utilization of new-generation DES and dual antiplatelet therapy, stent-related adverse events continue to persist and have not shown a plateau over time, in contrast to *de novo* coronary lesions [2-5].

Drug-Coated Balloon (DCB) treatment has demonstrated noninferior clinical outcomes when compared to DES implantation for In-Stent Restenosis (ISR) and *de novo* small vessel disease, as supported by existing evidence [6-8]. Recent trials have also shown the feasibility of utilizing DCB treatment in larger vessels, given appropriate predilation techniques [9,10]. The recommendations provided by the International Consensus Group and the Asian Pacific Consensus Group reports suggest that a DCB approach for native lesions is feasible and should be considered in cases where residual stenosis is less than 30% of the vessel diameter and no major dissections are observed [11-16]. Building upon these recommendations, the authors of this study have previously reported on the implementation of DCB-only treatment for LM disease in case reports [17-19]. Therefore, the objective of this study was to assess the impact, in terms of in-hospital and one-year clinical outcomes, of adopting a DCB treatment for unprotected LM coronary artery disease.

MATERIALS AND METHODS

Study patients

This retrospective registry included 42 consecutive patients with significant unprotected LM coronary artery stenosis capable of PCI from May 2018 to December 2020 (Impact of Drug-coated Balloon Treatment in *de Novo* Coronary Lesion; NCT04619277). The subjects of this study had to have all four of the following conditions:

(1) Clinical symptoms or objective evidence of myocardial ischemia during an exercise test; (2) angiographic evidence of ≧ 50% diameter stenosis of the LM by visual estimation; (3) suitable anatomy and lesion characteristics for PCI and preference by the patient and by the operator for a PCI with both being aware of the procedural risks; and (4) visual residual stenosis of ≤ 30% without flow-limiting dissection after pre-balloon angioplasty. Procedural success is defined as technical success with no in-hospital Major Adverse Cardiac Events (MACE). The trial protocol was approved by the institutional review board at participating site, and all patients provided written informed consent at the time of enrollment.

DCB-based procedure

The interventional approach was a composite of two steps according to the reports of DCB Consensus Groups [12-20]. First, semi or noncompliant balloons were used to prepare lesions with a balloon-to-artery ratio up to 1.0. Scoring balloon or rotablation were the optional choices for lesion preparation if a lesion had heavy calcification that is too hard for dilation. After predilation that was a fully inflated balloon of the correct size for the reference vessel, the lesion was reevaluated by several factors: (1) ≤ 30% residual stenosis, (2) thrombolysis in myocardial infarction flow grade 3, and (3) the absence of a flow-limiting dissection. DCB treatment was performed through an interventional

approach when all of the above three angiographic factors were satisfied as a result of balloon angioplasty. The DCB inflation time was recorded from the entry time of the DCB into the guide catheter until the time point of DCB inflation. DCB was inflated at least 30-60 seconds and kept as long as possible, considering the patient's symptoms to maximize drug delivery. If the inflation time was 30 seconds, it was inflated once more for a total of 60 seconds in all patients treated with DCB. The treatment plan was leaning toward DES implantation when patients had suboptimal angiographic results after predilation. According to this strategy, 23 patients were eventually treated with DCB (SeQuent® Please; B. Bruan Melsungen AG, Berlin, Germany) and 19 patients had second-generation DES (Resolute Onyx; Medtronic, Minneapolis, MN, USA) implantation.

Quantitative coronary angiography and follow-up data

The angiographic outcome in patients treated with DCB was assessed through Quantitative Coronary Angiography (QCA). QCA was analyzed off-line by a single independent expert in blinded core lab, using the validated software (CAAS II, Pie Medical Imaging). Binary restenosis was defined as at least 50% Diameter Stenosis (DS) at angiographic follow-up. Late Lumen Loss (LLL) is defined as the angiographic Minimal Lumen Diameter (MLD) immediately after DCB treatment minus the MLD at angiographic follow-up [21]. Therefore, the minus value of LLL was defined as luminal increase. Clinical follow-up was performed in all 42 patients after the index procedure. 23 treated with DCB was encouraged to receive scheduled angiographic follow-up after 6 months. The occurrence of MACE was assessed which was composed of cardiac death, nonfatal Myocardial Infarction (MI), stroke, and Target Lesion Revascularization (TLR) at the follow-up period.

Statistical analysis

Analyses were performed on a per-patient basis for clinical characteristics and outcomes (and its components) and a per-vessel basis for vessel-related parameters and vessel-level clinical outcomes. Categorical variables are presented as the 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. All probability values were two-sided, and P values <0.05 were considered statistically significant. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics

Baseline patient characteristics are shown in Table 1. The mean age of the patients was 65 years old and most of the patients were men. More patients with dyslipidemia in the DCB group and more current smokers in the DES group. In the clinical presentation, stable angina and acute coronary syndrome were 23.8% and 76.2%, respectively. There were 3 patients with AMI in the DES group as shown in Table 1.

Table 1. Patients characteristics.

	Total	DCB-only	DES-only	P value
	N=42 patients	N=23 patients	N=19 patients	
Age, years	65.2 ± 10.1	63.4 ± 10.9	67.4 ± 8.8	0.2
Men	32 (76.2)	17 (73.9)	15 (78.9)	0.703
Hypertension	23 (54.8)	15 (65.2)	8 (42.1)	0.134
Dyslipidemia	36 (85.7)	22 (95.7)	14 (73.7)	0.043
Diabetes	13 (31.0)	5 (21.7)	8 (42.1)	0.155
Current smoker	13 (31.0)	4 (17.4)	9 (47.4)	0.037

Previous myocardial infarction	1 (2.4)	1 (4.3)	0	0.358
Previous percutaneous coronary intervention	4 (9.5)	2 (8.7)	2 (10.5)	0.841
Previous coronary artery bypass grafting	0	0	0	
Previous stroke	1 (2.4)	1 (4.3)	0	0.358
Left ventricular ejection fraction, %	57.6 ± 10.7	58.9 ± 9.8	56.3 ± 11.5	0.46
Clinical presentation				0.141
Stable angina	10 (23.8)	6 (26.1)	4 (21.0)	
Unstable angina	29 (69.1)	17 (73.9)	12 (63.2)	
Acute myocardial infarction	3 (7.1)	0	3 (15.8)	

Note: Values are mean ± SD or number (percentage); DCB: Drug-Coated Balloon; DES: Drug-Eluting Stent.

Angiographic procedural data

Table 2 summarizes the angiographic and procedural data. The median SYNTAX score was 20.1 (interquartile range [IQR], 17.0-28.1) and the DES group was 27.5 (IQR, 20.0-30.0), which was higher than DCB group of 19.0 (IQR, 16.0-24.0). Most of the LM diseases were bifurcation lesions. The device diameter was larger in the DES group (3.5 ± 0.3 mm and 3.7 ± 0.4 mm, p=0.003). No bailout stenting was noted in the DCB group. Representative images of the impact of DCB-only treatment on *de novo* LM disease are shown in Table 2 and Figure 1.

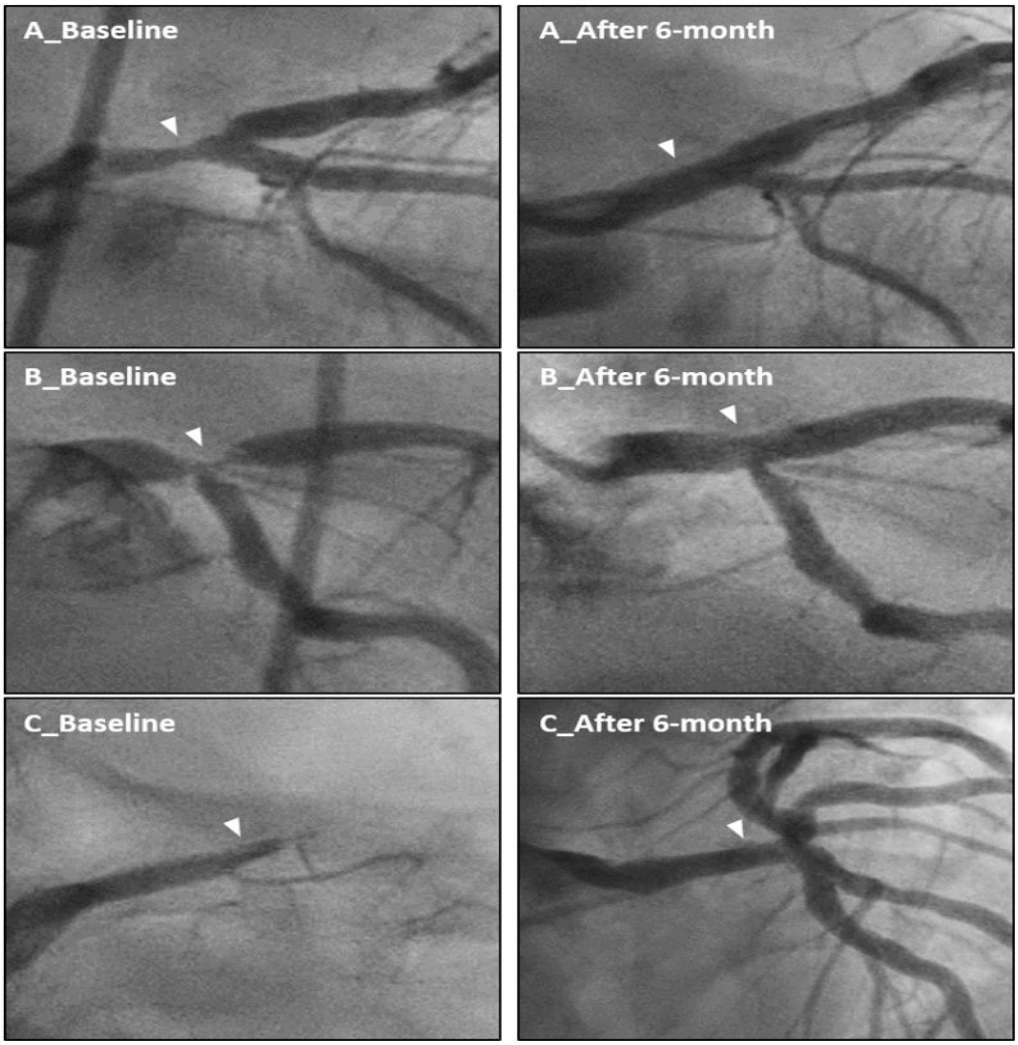
Table 2. Angiographic and procedural data.

	DCB-only	DES-only	P value
	N=23 patients	N=19 patients	
SYNTAX score, median (IQR)	19.0 (16.0-24.0)	27.5 (20.0-30.0)	0.007
Left main disease with right coronary artery stenosis	12 (52.2)	13 (68.4)	0.286
Left main lesion location			0.215
Ostium	1 (4.3)	4 (15.8)	
Body	2 (8.7)	4 (15.8)	
Bifurcation	22 (95.6)	18 (94.7)	
Chronic total occlusion	3 (13.0)	2 (10.5)	0.999
Scoring pre-balloon used	18 (78.3)	10 (52.6)	0.079
Device			
Diameter, mm	3.5 ± 0.3	3.7 ± 0.4	0.003
Length, mm	27.4 ± 8.9	33.3 ± 15.6	0.153

Device inflation time, second	63.9 ± 16.5	-	
Number of devices used	1.1 ± 0.3	1.4 ± 0.7	0.107
Intravascular ultrasound used	13 (56.5)	16 (84.2)	0.093
Fractional flow reverse used	6 (26.1)	2 (10.5)	0.258
Bail-out stenting	0	0	

Note: Values are mean ± SD or number (percentage); DCB: Drug-Coated Balloon; DES: Drug-Eluting Stent; SYNTAX: SYNergy between PCI with TAXUS and Cardiac Surgery; IQR: Interquartile Range.

Figure 1. Representative DCB-only treatment cases for unprotected LM disease. (A) LM shaft lesion; (B) LM bifurcation lesion; (C) LM chronic total occlusion lesion. **Note:** Arrowheads: LM stenotic lesions before procedure or 6-month after DCB treatment.



Clinical outcomes

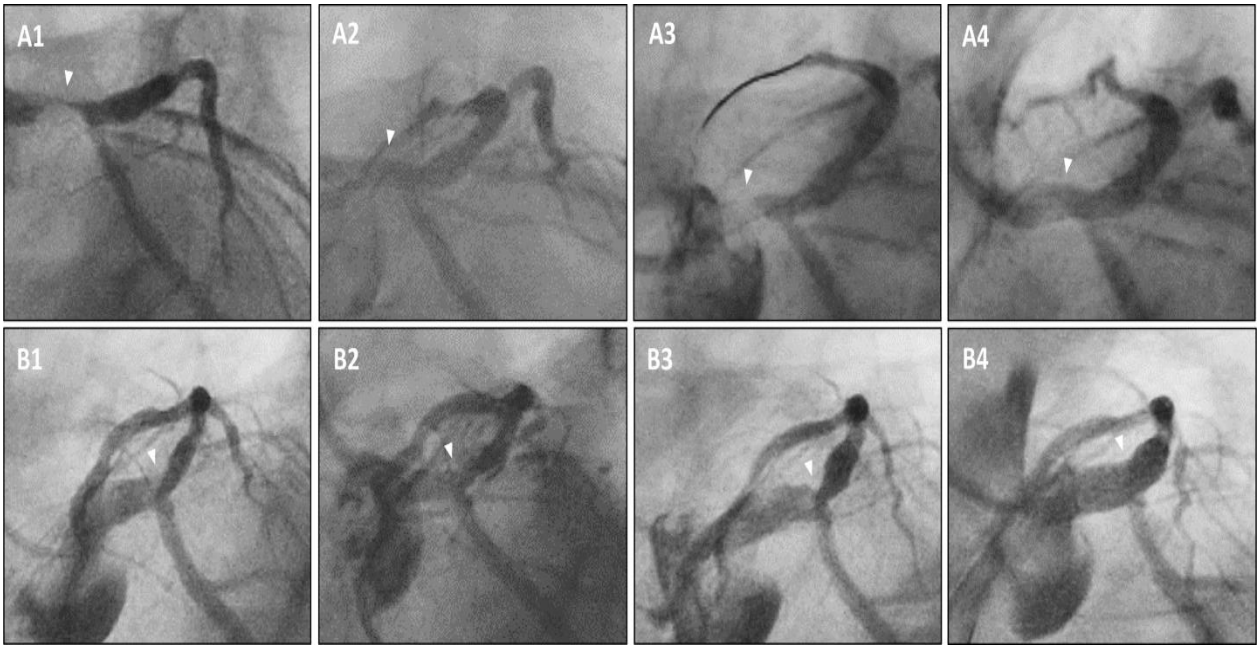
Table 3 summarizes in-hospital and 1-year clinical outcomes. The procedural success rate was 100% and 95% in the DCB and DES groups, respectively. The patient who failed the procedure had ST-segment elevation MI and expired several hours after DES implantation. Major in-hospital complications including cardiac death, emergency coronary bypass surgery, MI, target lesion thrombosis and stroke did not occur after DCB treatment. Clinically-driven target lesion revascularization was observed in two of 23 patients (8.7%) in the DCB group at 1-year follow-up. One TLR case was a 45-year-old man who was a current smoker and presented with unstable angina. The patient had 82% DS in the LM shaft and ostium. Successful pre-balloon angioplasty followed by a DCB treatment was performed. After 172 days, the patient revisited the hospital of the current study due to typical angina and his treadmill test was positive. The patient had poor medical compliance and was found to have voluntarily discontinued dual antiplatelet therapy after discharge. Considering his poor compliance, we treated the lesion again with a DCB as shown in Table 3 and Figure 2.

Table 3. In-hospital and 1 year clinical outcomes.

	DCB-only	DES-only
	N=23 patients	N=19 patients
In-hospital clinical outcomes		
Cardiac death	0	1 (5.3)
Emergency coronary artery bypass grafting	0	0
Myocardial infarction	0	0
Target lesion thrombosis	0	0
Stroke	0	0
1 year clinical outcomes including in-hospital period		
Major adverse cardiac events	2 (8.7)	2 (10.5)
Death	0	2 (10.5)
Cardiac death	0	1 (5.3)
Coronary artery bypass grafting	0	0
Myocardial infarction	0	0
Clinically driven target lesion revascularization	2 (8.7)	0
Clinically driven target vessel revascularization	2 (8.7)	0
Target lesion thrombosis	0	0
Stroke	0	1 (5.3)
Major bleeding (BARC type 3,5)	0	1 (5.3)

Note: Values is number (percentage). Major adverse cardiacevents were composed of cardiac death, non-fatal myocardial infarction, stroke, and target lesion revascularization.

Figure 2. Clinically-driven TLR cases in the DCB. (A) LMshaft and ostial lesion occurred at 172 days after DCB treatment. This patient was poor medication adherent, and revascularization was performed again through a 3.5 × 20 mm DCB; (B) Distal LM and left anterior descending ostial lesion occurred at 300 days after DCB treatment. This lesion was treated with a 4.5 × 18 mm DES. **Note:** Number 1: Pre-procedure; Number 2: Post-procedure; Number 3: Follow-up angiography at 6 months; Number 4: After target lesion revascularization; Arrowheads: LM lesions sites.



The patient has been currently well without angina for 17 months [18]. The other TLR case, a 56-year-old man who was diagnosed with unstable angina. The patient had 66% DS with distal LM including the ostium of the left anterior descending. Pre-balloon angioplasty was performed followed by DCB treatment. After 300 days, this patient revisited the hospital of the current study due to stable angina and positive exercise treadmill test. The ostium of the left anterior descending artery developed stenosis again and the lesion was successfully treated with a DES (Figure 2B). The patient has been well without angina for 12 months now. One event of major bleeding (BARC type 5; intracranial hemorrhage) was noted 340 days after the procedure in the DES group.

Serial quantitative coronary angiographic results of DCB treatment patients

The mean reference vessel diameter, MLD, and DS at the baseline were 3.1 ± 0.4, 0.9 ± 0.4, and 72.4% ± 13.2%, respectively, in the DCB group (Table 4). Immediately after DCB treatment, comparable increases and decreases in MLD and DS, respectively, were noted. In addition, the average of acute lumen gain after DCB treatment was 1.3 ± 0.5 mm. After DCB treatment, 19 of the vessels (82.6%) had dissections (type A=ten patients; type B=five patients; type C=four patients). Moreover, 15 (65.2%) patients returned for scheduled follow-up angiography at a median of 194 days (IQR, 182-287 days) after the index procedure, ensuring that serial QCA data were available in the DCB group. In comparison with the post-DCB treatment and follow-up, the result shows similar MLD (2.2 ± 0.3 mm *vs* 2.2 ± 0.5 mm) and DS (30.1 ± 8.4% *vs*. 31.4 ± 13.7%), respectively. A luminal increase was found in 46.7% (n=7) and the mean of the LLL was found to be 0.07 ± 0.45 mm. All dissections disappeared at the follow-up coronary angiography. Two cases of binary restenosis in the DCB group were noted and were retreated with DCB and DES, respectively (Figures 2A and 2B) as shown in Table 4.

Table 4. Serial quantitative coronary angiographic results of DCB-only treatment patients.

Baseline	N=23 patients
Reference vessel diameter, mm	3.1 ± 0.4
Minimal lumen diameter, mm	0.9 ± 0.4
Diameter stenosis, %	72.4 ± 13.2
Lesion length, mm	22.9 ± 9.3
Post-DCB treatment	N=23 patients
Minimal lumen diameter, mm	2.2 ± 0.3
Diameter stenosis, %	30.1 ± 8.4
Acute lumen gain, mm	1.3 ± 0.5
Follow-up	N=15 patients
Minimal lumen diameter, mm	2.2 ± 0.5
Diameter stenosis, %	31.4 ± 13.7
Late lumen loss, mm	0.07 ± 0.45
Net lumen gain, mm	1.6 ± 0.8
Binary restenosis	2 (13.3)
Follow-up duration, day, median (IQR)	194 (182-287)
Note: Values are mean ± SD or number (percentage); DCB: Drug-Coated Balloon; IQR: Inter Quartile Range.	

DISCUSSION

The findings of this study suggest that the use of DCB as the sole treatment modality may be a safe and effective therapeutic approach for patients with LM disease, especially when combined with successful predilation. The absence of major adverse events, such as cardiac death or MI, during the follow-up period further strengthens the feasibility of this treatment strategy, even in patients with complex clinical presentations and lesion subsets in LM disease.

Balloon angioplasty serves as the fundamental mechanism underlying DCB treatment. In the BENESTENT 1 and 2 studies, the occurrence of hard endpoints such as death and MI did not exhibit significant differences between balloon angioplasty and bare-metal stent implantation for stable angina patients [22,23]. However, it is important to note that balloon angioplasty performed on LM coronary artery disease patients is associated with relatively higher rates of repeat revascularization, primarily due to thrombosis, which significantly contributes to acute vessel closure subsequent to balloon angioplasty [24,25]. The development of catheter technology and the utilization of more potent antithrombotics, including P2Y12 inhibitors, have resulted in a reduction of safety concerns associated with percutaneous coronary angioplasty, such as acute vessel closure. Nonetheless, it remains uncertain whether DCB treatment can be safely extended to patients with LM disease. The authors of the present study were pioneers in implementing DCB-only treatment for LM disease, as evidenced by previous case reports [17-19]. This study aimed to evaluate the feasibility and safety of DCB-only treatment in a broad population of LM disease patients eligible for PCI during the 21st century era. More than half of the LM disease patients exhibited suitability for DCB treatment, and no in-hospital adverse events, including acute vessel closure, were observed, contrary to initial concerns. In the present study, meticulous clinical follow-up with telephone interviews and outpatient clinic visits revealed MACE in four (9.5%, two patients per group) of 42 patients.

One fatal cerebral hemorrhage occurred at 1 year in patients who underwent DES implantation. Within the DCB group, two patients experienced TLR, both of whom presented with stable angina. These patients underwent successful repeat revascularization procedures using either DCB or DES treatments. Among the cases of TLR, one instance involved stenosis occurring in the ostium of the LM, while the other occurred in the ostium of the left anterior descending artery. It is worth noting that ostial lesions tend to have a higher recurrence rate following PCI when compared to non-ostial lesions [26,27]. In this study, both TLR cases were associated with ostial lesions. Consequently, the selection of a device specific to the lesion should be carefully considered.

A luminal increase was found in 46.7% (n=7) and net lumen gain (follow-up MLD minus baseline MLD) was 1.6 ± 0.8 mm in the DCB group. Paclitaxel administration to the vascular wall could have additional effects beyond neointimal growth reduction by inhibition of smooth muscle cell proliferation[28]. Human studies have demonstrated that the administration of high concentrations of paclitaxel directly to the vessel walls leads to a reduction in plaque burden and an increase in vessel size [29,30]. Furthermore, the local delivery of paclitaxel to carotid arteries has been found to promote vessel enlargement and reduce neointimal growth [31].

Despite the reduction in the risk of stent thrombosis with the development of DES, the occurrence of stent thrombosis in the LM remains a critical concern due to the large amount of myocardium at risk. Furthermore, major bleeding events, particularly in high bleeding risk patients, pose a significant challenge. The optimal duration of dual antiplatelet therapy following LM stenting remains unclear. This creates a clinical dilemma for physicians, as a careful balance between the risks and benefits of DAPT continuation is necessary to prevent stent thrombosis while avoiding major bleeding events in LM disease patients. Consequently, this study proposes that DCB treatment could serve as a potential option for LM disease, aiming to minimize potential long-term safety concerns.

Study limitations

Our study has several limitations. First, the population comes from an expert center in DCB treatment for LM. Thus, it may not be reproducible everywhere without an adequate learning curve. Second, intravascular ultrasound-guided approaches were in only 13 (56.5%) patients in the DCB treatment group. However, six patients were treated with fractional flow reserve-guided DCB to ensure safety. Third, although the inflation time of each DCB was correctly between 30 and 60 seconds, this could be critical in patients with impaired Left Ventricular Ejection Fraction (LVEF). In this study, however, the average LVEF of the DCB treatment group was 58.9 ± 9.8%. In accordance with the recommendations provided by the International Consensus Group and the Asian Pacific Consensus Group reports, the treatment approach of either DCB or DES was determined based on the provisional strategy following predilation. This approach is considered the primary contributing factor for the absence of bailout stenting in this study. However, larger-scale noninferiority clinical trials are required to assess the long-term outcomes following DCB treatment for LM coronary artery stenosis.

CONCLUSION

In conclusion, this study implies that utilizing DCB as the sole treatment approach for LM disease might be both safe and effective, specifically in patients who are carefully selected and exhibit favorable predilation outcomes. The notable rate of successful procedures and the absence of significant adverse events point towards the potential of this DCB-based treatment modality as a viable alternative for managing LM disease. However, further prospective studies are necessary to validate these findings, particularly in terms of long-term outcomes, and to establish the optimal criteria for patient selection.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived due to the observational retrospective nature of the study.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study at the time of enrollment.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The data underlying this article will be shared on reasonable request to the corresponding author

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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