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ORIGINAL PAPER

12-Month clinical results of drug-coated balloons for de novo coronary lesion in vessels exceeding 3.0 mm

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Abstract

The purpose of this observational study was to investigate the feasibility, initial safety, and efficacy of the SeQuent® Please DCB (B. Braun Melsungen, Germany) for patients with de novo coronary lesions in vessels exceeding 3.0 mm in a consecutive series of all comer percutaneous coronary intervention. A total of 120 patients (135 lesions) with de novo coronary lesions in vessels ≥ 3.0 mm treated with DCB were enrolled in this single-centre prospective observational study. The primary endpoint was target lesion failure (TLF), a composite endpoint of cardiac death, target vessel-myocardial infarction (TV-MI), and clinically driven target vessel revascularization (TLR) at 12 months. Safety endpoints included cardiac death, TV-MI, and definite target vessel thrombosis. 45.9% of the lesions were classified as complex (type B2/C). The reference vessel diameter was 3.09 ± 0.31 mm measured via quantitative coronary angiography analysis. Coronary dissections occurred in 42 patients (35.0%; Type A-B 14.1%; Type C 19.1%; Type D: 1.6%), two of which [1.6%; (type D dissection)] underwent bail-out stent implantation. 12-month follow-up was completed in 100% patients. The 12-month incidence of TLF was 3.4%. The clinically driven TLR occurred in four patients (3.4%). The incidence of TLR was low in patients without any detectable dissections, similar to those with dissections (3.8% vs. 2.5%; p = 0.146). No patient suffered cardiac death, TV-MI, or target vessel thrombosis. The study shows the feasibility, initial safety, and efficacy of coronary intervention using SeQuent® Please DCB for the treatment of patients with de novo lesion in vessels exceeding 3 mm. The study highlights that the coronary dissection (Type A–C) post DCB treatment occurs frequently but is safe at follow up.

Keywords Drug-coated balloon · De novo · Target lesion failure · Coronary dissection

Introduction

Drug-eluting stents (DES) significantly reduce angiographic restenosis and recurrent ischemia necessitating repeat intervention in patients with coronary artery disease [1, 2]. However, permanent metallic stenting may result in jailed side branches, prevent expansive remodelling, and eliminate reactive vasomotion. Furthermore, several problems remain, such as stent fracture, in-stent neo-atherosclerosis, and very late stent thrombosis [3]. A possible solution to overcome this problem could be a "stent-less" percutaneous coronary intervention (PCI) with drug-coated balloon (DCB) in both clinical and angiographic conditions that require the avoidance of stent implantation. However, clinical applications of this novel technology for de novo coronary lesions are currently limited to small vessels below 2.8 mm in diameter [4–6] and other particular scenarios, such as patients at high risk of bleeding [7], coronary bifurcation lesions [8], acute myocardial infarction [9], and diffuse disease [10].

Existing evidence indicated that DCB may be an acceptable alternative to DES in the treatment of some patients with small de novo coronary lesions [11, 12]. In a recent observational study [13], Cortese et al. demonstrated superior

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outcomes for 156 patients with native coronary lesions treated with DCB angioplasty at the 9-month follow-up. Nonetheless, there was a paucity of clinical feasibility and performance of DCB treatment for de novo coronary lesion in vessels with diameters exceeding 3.0 mm.

In a Drug-coatEd BAlloon angioplasTy for de novo coronary lesion in vessels largEr than 3.0 mm (DEBATE) trial, we investigated the feasibility, initial safety, and efficacy of the SeQuent® Please drug-coated balloon (DCB, B. Braun Melsungen, Germany) when treating patients with de novo coronary lesions in vessels with diameters exceeding 3.0 mm in a real-world setting.

Methods

Study population

Data in the DEBATE trial were prospectively collected for patients with de novo coronary lesions treated with SeQuent® Please DCB angioplasty in Xijing Hospital (Xi'an, China) between January 2016 and June 2017. Patients (n = 120) with age > 18 years and symptomatic coronary artery disease with de novo lesions in one or two native coronary arteries (vessel diameter exceeding 3 mm by visual estimation) were included. The major exclusion criteria included patients with acute myocardial infarction within 1 week, cardiac shock because of its high mortality [14], left ventricular ejection fraction (LVEF) < 35%, estimated glomerular filtration rate < 30 ml/min, in-stent restenosis lesions, ostial lesions, lesions located in left main coronary artery or vessel size < 3.0 mm (via visual estimation). We also restricted the use of DCB in case of severely tortuous and calcified or angulated vessels, especially when vessel recoil seemed possible. The study was approved by the local ethical review board at Xijing Hospital.

Study devices

In the current study, the SeQuent® Please DCB (B. Braun Melsungen, Germany) was used. The SeQuent® Please DCB is coated with 3 μg of paclitaxel/mm^2 of balloon surface. The balloon was inflated one time. During this inflation, more than 90% of the drug is released [15]. The SeQuent® Please DCB is available in diameters of 2.75, 3.0, 3. 5, and 4.0 mm and in lengths of 10, 15, 17, 20, 26, and 30 mm.

Lesion preparation and DCB procedure

The intervention was performed according to international guidelines and the recent consensus on DCB treatment [10]. Pre-dilation was mandatory to obtain minimal residual stenosis. Briefly, a semi-compliant balloon (≤2.5 mm) with moderate pressure (8–14 atm) was adopted to dilate the target lesion. In case of significant residual stenosis, a non-compliance balloon and/or cutting balloon (the recommended size was 0.8 to 1.0:1 of DCB) was used to adequately dilate the lesion. If acceptable angiographic results were obtained (i.e., Thrombolysis In Myocardial Infarction [TIMI] 3 flow and residual stenosis < 30%), the DCB was inflated by nominal pressure for at least 30 s with an overlap larger than 2 mm on each edge of the pre-dilation balloon-treated segment. The DCB was sized to vessel diameter in a 1:1 ratio. In case of flow-limiting dissection or major dissection (type D or higher) after pre-dilation or unsatisfactory results (even post-DCB treatment), a stent PCI with DES was recommended. Device success was defined as the attainment of < 50% residual stenosis of the target lesion using only the studied DCB. Clinical success was defined as attainment of < 50% residual stenosis by visual estimate, TIMI 3 flow, and no in-hospital major adverse cardiac event (defined as any occurrence of target lesion revascularization [TLR], ST-segment elevation acute myocardial infarction, or cardiac death). A case example of the DCB application is illustrated in Fig. 1.

Medication

All enrolled patients were pre-treated with aspirin (100 mg/day) and clopidogrel (300–600 mg loading dose, followed by 75 mg daily) or ticagrelor (180 mg loading dose, followed by 90 mg twice per day). Intravenous heparin was used to maintain an activated clotting time between 250 and 300 s for procedural anticoagulation. Dual antiplatelet therapy (DAPT) post procedure was recommended for at least 3 months, followed by aspirin indefinitely.

Quantitative coronary angiography

Angiographic measurements were conducted offline with the QAngio XA software (version 7.3, Medis, Leiden, the Netherlands). Angiographic measurements were done separately at the target lesion over the entire length of the study device, within 5 mm proximal and distal of the target lesion, and over the entire segment.

Study endpoints and definitions

All patients were followed up via telephone or hospital visit at the 12 months follow-up. The primary endpoint was the incidence of target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, and clinically driven TLR at 12 months. Safety endpoints included cardiac death, TV-MI, and definite target vessel thrombosis. Death was considered to be of cardiac cause unless a non-cardiac cause was specifically identified. All myocardial infarction

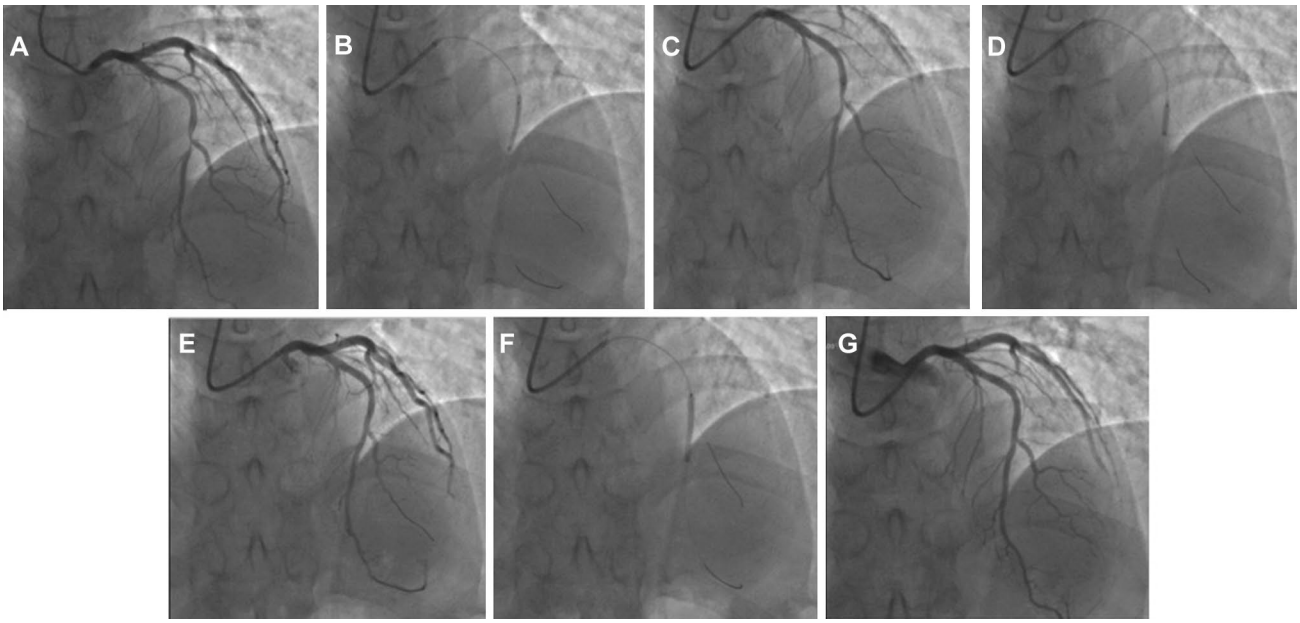

Fig. 1 A case example of DCB application. **a** Initial angiogram, **b** pre-dilation with a 2.0*20 mm semi-compliance balloon, **c** result after dilation with semi-compliance balloon, **d** pre-dilation with 3.0*10 mm cutting balloon, **e** result after dilation with cutting balloon, **f** treatment with 3.0*26 DCB, **g** final result after DCB treatment

data were reported based on extended historical definitions [16]. Target lesion revascularization (TLR) was defined as any clinically driven repeat revascularization caused by a > 50% stenosis within DCB treated segment or within a 5-mm border proximal or distal to the DCB site. Definite target vessel thrombosis was classified according to the Academic Research Consortium. All events were adjudicated by an independent clinical event committee.

Statistical analysis

Continuous variables are shown as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as counts and percentages of the total. The differences between groups were compared via the χ^2 test or the Fisher exact test for categorical variables, and the Student *t* test or the Wilcoxon rank-sum test scores where appropriate for continuous variables. Statistical significance was defined at a two-sided p-value < 0.05. All analyses were undertaken using SPSS 21.0 (IBM Corp., Armonk, New York, USA).

Results

Patient demographics

A total of 120 patients with 135 de novo coronary lesions in vessels with a diameter exceeding 3.0 mm were included in the current study. The patient demographics are shown in Table 1. The mean age was 57.64 ± 11.35 years and 78.3% were male. Systemic hypertension was observed in 48.3% of the patients, diabetes mellitus in 30.8%, smoking in 40.8%, and hyperlipidemia in 26.6%. 15.8% had already undergone PCI and 1.6% had been submitted to CABG prior to index procedure. The clinical presentation prior to DCB treatment was of stable angina in 12.5%, unstable angina in 72.5%, and acute myocardial infarction in 15.0%.

Lesion and procedure characteristics

The lesion characteristics are shown in Table 2. 45.9% of the lesions were classified as complex (American College of Cardiology/American Heart Association type B2/C). The majority of lesions (87.4%) involved major epicardial arteries and more than half addressed were in the left anterior descending (64.4%). Quantitative coronary angiography (QCA) analysis indicated a reference vessel diameter of 3.09 ± 0.31 mm with a length of 17.49 ± 7.80 mm. The procedural data were presented in Table 3. With regard to the lesion preparation, a semi-compliant balloon was used in 38.3% of the patients, a non-compliant balloon in 54.1%, and a cutting balloon in 78.3% (diameter: 2.89 ± 0.41 mm, length: 9.38 ± 1.54 mm). The dimensions of the utilized DCB were 3.22 ± 0.30 mm in diameter and 23.52 ± 5.49 mm in length. DCB inflation duration and pressure were 57.59 ± 7.47 s and 8.05 ± 1.79 atm, respectively. Angiographically detectable dissection was

Table 1 Patient demographics

Variable	All patients (N = 120)
Age (years)	57.64 ± 11.35
Male gender	94 (78.3%)
Diabetes	37 (30.8%)
Insulin-treated diabetes mellitus	14 (37.8%)
Hypertension	58 (48.3%)
Hyperlipidemia	32 (26.6%)
History of smoking	49 (40.8%)
Prior PCI	19 (15.8%)
Prior CABG	2 (1.6%)
Peripheral vascular disease	6 (5.0%)
Atrial fibrillation	4 (3.3%)
Stable angina	15(12.5%)
Unstable angina	87(72.5%)
NSTEMI	7 (5.8%)
STEMI	11 (9.1%)
Anterior STEMI	9 (7.5%)
Grace score	130.42 ± 31.99
Median troponin I (ng/ml)	0.008 (0.002, 0.027)
Median CK-MB	1.40 (1.00, 2.15)

Data presented as mean ± standard deviation, median [interquartile range (IQR)] or n (%)

PCI percutaneous coronary intervention, *CABG* coronary artery bypass graft, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

Table 2 Lesion characteristics

Variable	All lesions
Number of lesions	135
Target vessel	
LAD	87 (64.4%)
RCA	25 (18.5%)
LCX	23 (17.0%)
Location	
Major epicardial vessel lesion	118 (87.4%)
Side branch lesion	17 (12.6%)
AHA lesion classification (B2/C)	62 (45.9%)
Calcification	10 (7.4%)
Chronic total occlusion	4 (3.0%)
Bifurcation	18 (13.3%)
Reference diameter (mean ± SD, mm)	3.09 ± 0.31
Lesion length (mean ± SD, mm)	17.49 ± 7.80
Degree of stenosis (area, mean ± SD, %)	85.31 ± 10.13
Degree of stenosis (diameter, mean ± SD, %)	64.54 ± 14.60

Data presented as mean ± standard deviation or n (%)

LAD left anterior descending, *RCA* Right coronary artery, *LCX* left circumflex

Table 3 The procedural data and medications therapy at discharge

Variable	All patients (N = 120)
Number of lesions	135
Compliance balloon (%)	46 (38.3%)
Compliance balloon (mean ± SD, mm)	2.16 ± 0.34
NC balloon (%)	65 (54.1%)
NC balloon diameter (mean ± SD, mm)	2.89 ± 0.41
NC balloon length (mean ± SD, mm)	13.57 ± 1.90
Cutting balloon (%)	94 (78.3%)
Cutting balloon diameter (mean ± SD, mm)	2.94 ± 0.36
Cutting balloon length (mean ± SD, mm)	9.38 ± 1.54
DCBs used	135
DCBs per patient	1.12
DCB diameter (mean ± SD, mm)	3.22 ± 0.30
DCB length (mean ± SD, mm)	23.52 ± 5.49
DCB inflation pressure (mean ± SD, atm)	8.05 ± 1.79
DCB inflation time (mean ± SD, s)	57.59 ± 7.47
Dissection	42 (35.0%)
Dissection A	8 (6.6%)
Dissection B	9 (7.5%)
Dissection C	23 (19.1%)
Dissection D	2 (1.6%)
Bail-out stenting with stents	2 (1.6%)
Acute luminal gain (mean ± SD, mm) by QCA	1.29 ± 0.53
Final stenosis (mean ± SD, %)	22.87 ± 7.64
Device success	98.3%
Procedural success	100%
Dual antiplatelet therapy at discharge	
Aspirin	120 (100.0%)
Clopidogrel	71 (59.2%)
Ticagrelor	49 (40.8%)
Other therapies at discharge	
Statins	120 (100.0%)
Beta blockers	102 (85.0%)
ACEI/ARB	90 (75.0%)

Data presented as mean ± standard deviation or n (%)

NC balloon non-compliance balloon, *DCB* drug-coated balloon, *QCA* quantifying coronary angiograph, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

observed in 35.0% of patients (type A-B: 14.1%, type C: 19.1%, and type D: 1.6%). Bail-out stenting was required in two patients (1.6%) due to type D dissection. Residual stenosis was 22.87 ± 7.64% by QCA. The acute luminal gain was 1.29 ± 0.53 mm. Device success was 98.3% and clinical success was 100%. Regarding double antiplatelet therapy (DAPT), 40.8% of patients were discharged with the combination of ticagrelor plus aspirin, as reported in Table 3.

Clinical results at 12-month follow-up

Clinical follow-up was completed in all patients undergoing DCB treatment at the 12-month follow-up (n = 118). The clinical event data is shown in Table 4. During the follow-up period, the 12-month incidence of TLF was 3.4%. Total revascularization, clinically driven TLR, and target vessel revascularization (including TLR) occurred in 13 patients (11.0%), 4 patients (4.2%), and 6 patients (5.9%), respectively. No patient suffered cardiac death, TV-MI, or target vessel thrombosis.

Clinical prognosis of coronary dissections

In total, 42 patients had angiographically detectable dissections after DCB intervention and two received bail-out DES implantation. Out of four clinically driven TLR, three patients presented without dissection and one patient presented with dissection post procedure, respectively. The incidence of TLR was low in patients without any detectable dissections, similar to those with type A, B, or C dissections (3.8% vs. 2.5%; p = 0.146). No patient with dissection suffered cardiac death, TV-MI, or target vessel thrombosis. A case example of TLR after DCB treatment with dissection is illustrated in Fig. 2. The patient presented a diffuse and bifurcation lesion in the LAD artery. The patient presented a type B dissection without limited flow after DCB treatment. At 6-month follow-up, the patient had a recurrent angina and the angiogram demonstrated that type B dissection worsened to type C dissection and multiple restenosis in the DCB treated lesion with limited flow. However, some type C dissections led to complete healing in patients undergoing angiography follow-up in the present study (Fig. 3). Our findings indicate that the prognosis of coronary dissections post DCB treatment may be complicated.

Table 4 The clinical event data

Variable	All patients (N = 118)
TLF	4 (3.4%)
Total revascularization	13 (11.0%)
TLR	4 (3.4%)
TVR (including TLR)	6 (5.1%)
Non-TLT and TVR	7 (5.9%)
TV-MI	0 (0%)
All-cause death	0 (0%)
Cardiac death	0 (0%)
Thrombosis	0 (0%)

Data presented as n (%)

TLF target lesion failure, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *TV-MI* target vessel-myocardial infarction

Discussion

For the first time, this prospective observational DEBATE study reports the feasibility, safety, and efficacy of DCB only angioplasty for patients with de novo lesions in vessels with a diameter exceeding 3.0 mm at the mid-term follow-up. The study has shown that coronary intervention using Sequent® Please DCB for patients with large de novo vessel disease is associated with low incidences of TLF and definite target vessel thrombosis. Furthermore, our results confirm that non-flow limiting coronary dissection (type A–C) post DCB treatment may not require further intervention.

Current clinical guidelines only support the use of DCB angioplasty for the treatment of de novo stenosis if the lesions are located at small coronary vessels [10]. Existing clinical trials had support the efficacy and safety of DCB in the treatment of small vessel de novo lesions. A subgroup analysis from the SeQuent SVD registry [17] demonstrated that treatment with DCB was associated with a similar risk of MACE (4.7%% vs. 4.0%, p = 0.866) and target vessel thrombosis (0.6% vs. 4.2%, p = 0.054) compared to DCB plus BMS in small coronary vessels at the 9-month follow-up. More specifically, the SCAAR (Swedish Coronary and Angioplasty Registry) study [18], which compared DCB against new generation DES, demonstrated a substantially lower risk for target vessel thrombosis for DCB compared to DES for the treatment of de novo coronary artery lesions after adjustment for baseline differences between both groups. Furthermore, low risk of clinical adverse events with DCB angioplasty in patients with native vessels, as seen in real-world registries [17, 19], seems particularly encouraging and tends to offset concerns of acute recoil, coronary dissections, and acute vessel closure.

Nevertheless, DCB cannot be a general substitute for DES, as DCB cannot overcome the main limitations of balloon angioplasty. Realistically, DCB treated lesions with good angiographic result after balloon dilation represent a natural selection of less complex lesions. In the OCTOPUS-2 study [20], Poerner et al. studied 46 patients with de novo lesions following fractional flow reverse guided DCB angioplasty in all-comers. The MACE rate was low (4.7%), and the lumen diameter showed a progressively increasing trend (late lumen loss: -0.13 ± 0.44 mm) without aneurysm formation or restenosis at 6-month follow-up. Similarly, Cortese et al. [13] studied 156 patients approximately 9 months after DCB angioplasty with limited exclusion criteria and a restrictive use of DCB and cases of big vessel size (e.g., > 3 mm in diameter). To the best of our knowledge, this is the first prospective, single centre registry that investigates the feasibility, safety, and efficacy

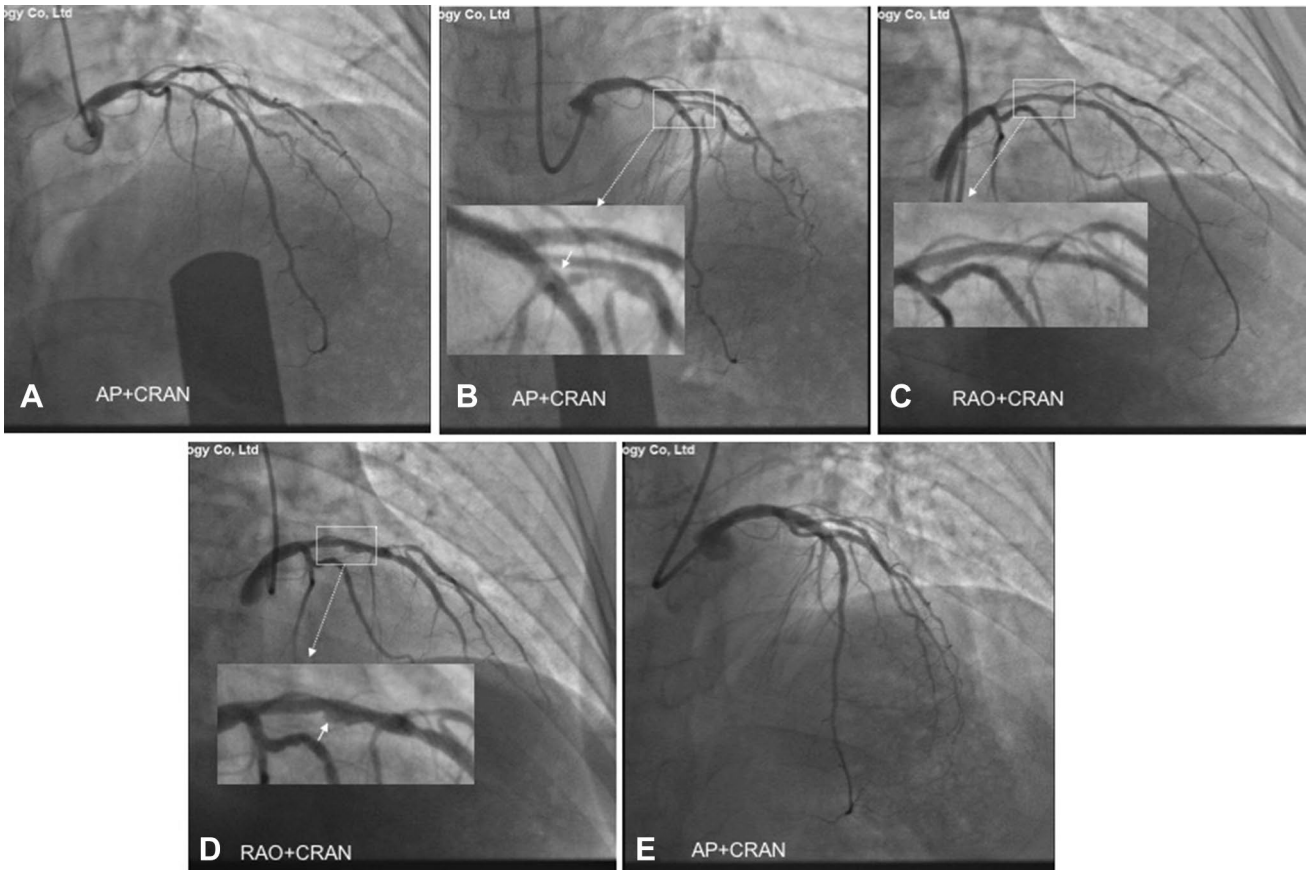

Fig. 2 A case example of TLR after DCB treatment presented with dissection. **a** The initial angiogram showed a long and bifurcation lesion in LAD, **b** final result after DCB treatment. The arrow indicates a type B dissection at the AP + CRAN view. **c** The type B dissection was invisible at the RAO + CRAN view. **d** The arrow indicates that the type B dissection worsened to a type C dissection and multiple restenosis in the DCB treated lesion with limited flow. **e** The stents were implanted in the LAD artery

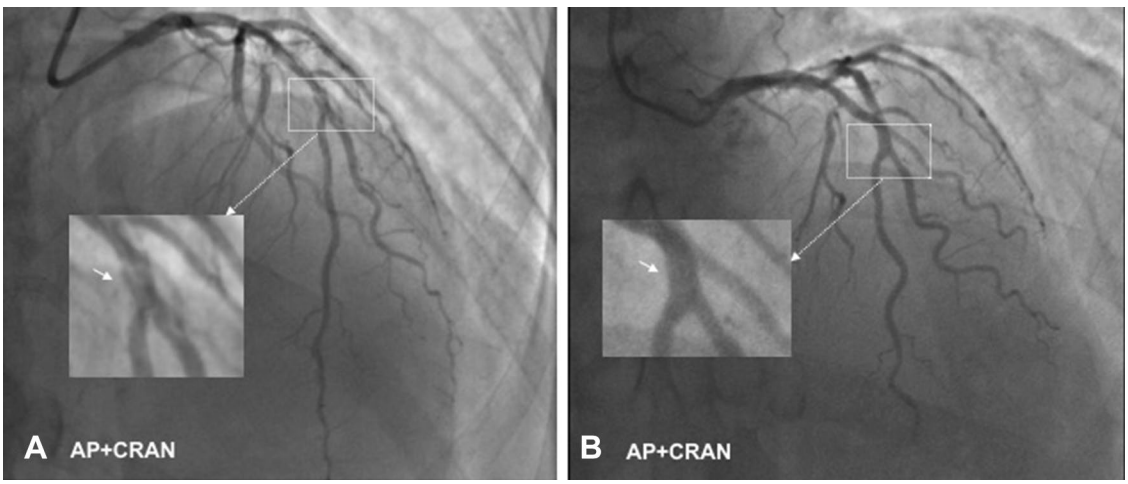

Fig. 3 A case example of completely healed type C dissection post DCB treatment at the 6-month angiograph follow up. **a** The arrow indicates a type C dissection, **b** the arrow indicates complete healing of the previous dissection

of DCB angioplasty in patients with de novo lesions in vessels with diameters exceeding 3.0 mm at 12-month follow-up. In particular, almost half of the treated lesions were classified B2/C, with a number of complex lesions presenting calcification, bifurcation, and/or chronic total occlusion. In addition, the majority of patients enrolled in the study were unstable before PCI, the use of DCB may be challenged for the high thrombotic risk. Fortunately, no patient suffered cardiac death, TV-MI, or target vessel thrombosis in our study. It may be explained by the fact that near half of patients received ticagrelor and two-thirds of lesions were pre-treated with cutting balloon.

Despite the encouraging outcomes of DCB for the elective stenotic de novo lesions only, the potential drawback of DCB is the acute vessel closure compared to metallic stents. However, the optimal strategy for the need of bail-out stenting when presenting dissection remains unclear and severe dissection can potentially lead to acute closure and subsequent myocardial infarction. Because of this concern, bail-out stents were implanted in two patients (1.6%) with type D dissection after lesion preparation in the current study. However, this percentage is significantly lower compared with previous studies, where bailout stenting ranged from 7.7% [21] to 12.3% [5]. This may be explained by an important difference between our study and previous ones: the bail-out stenting was only required in D–F dissection. Although two recent consensus documents [10, 22] recommend a standard approach with implantation of DES in case of flow-limiting dissection (NHLBI classification grade C–F) after pre-dilation in small coronary vessels and bifurcations, limited experience of the operator aggravates the decision whether to proceed with a DCB or to implant a DES in case of a major dissection in vessels with diameters exceeding 3.0 mm; hence, this remains an important issue.

Lesion preparation is a critical step in the DCB-only strategy. To ensure sufficient initial lumen gain, aggressive pre-dilation may result in severe dissection and leave stent-less treatment inaccessible for patients. In contrast, conservative lesion preparation is associated with reduced minimal luminal areas and over-residual plaque area, which emerged as predictors of restenosis. In the present study, all lesions were pre-dilated and cutting balloon (diameter: 2.94 ± 0.36 mm) was used in 78.3% of patients. Actually, leaving small dissections after DCB can heal well. Although the mechanism between adequate lesion preparation and low TLR incidence is not clear, it may be partly due to the late lumen enlargement, which was observed previously [23]. Therefore, we recommend sufficient luminal gain during the DCB procedure to reduce future restenosis unless flow-limiting dissection occurs.

No correlation between post-procedural coronary dissection type A-C on angiography examination and adverse clinical events in patients with de novo lesions treated with DCB only angioplasty has been found before [13]. In the present study, one-third of the patients had angiographically detectable dissections after DCB intervention; however, the incidence of TLR showed no significant difference compared to patients without dissection. These data are consistent with the study reported by Cortese et al. [13], who showed that leaving a non-flow-limiting dissection untreated after DCB angioplasty is safe and not associated with increased TLR. Moreover, repeat angiography at the 6-month follow-up showed that 93.8% of patients with type A-C dissection achieved complete vessel healing [13]. In the limited angiographical follow up cases of the present study, we found that a type B dissection worsened to type C dissection and some type C dissections completely healed. This indicated that the prognosis of coronary dissections post DCB treatment may be complicated. Further studies with a careful protocol, especially including intravascular imaging modalities pre-, post-produce, and at follow-ups, should be performed to obtain more confirmative information.

This preliminary observational study seems to show that DCB only for lesions involved major epicardial arteries is associated with favourable clinical outcomes at the mid-term follow-up. More studies need to be performed in the real-world clinical practice, to precisely determine the optimal indications of DCB only in patients with different clinical and anatomical scenarios. Furthermore, it is important to recognize the dissection types after pre-dilation, and appropriate suggestions should be provided to ultimately help interventionists with the selection of the optimal treatment choice. Prolonged dual antiplatelet therapy may help patients to avoid a thrombotic event. However, these patients remain at risk of acute vessel closure if coronary dissection is severe and tends to progress post-procedure. Primary care and intravascular imaging guided PCI may play an important role for reducing the potential risk of adverse events in patients with de novo lesions post DCB only treatment.

Study limitations

There are several limitations to our study that need to be considered. Firstly, as this was a single centre study with a small sample size, a prospective randomized multicentre trial with a large number of participants will be needed to confirm the value of DCB in de novo large vessel lesions. Secondly, the favourable results may not be reproducible everywhere without an adequate learning curve. Finally, although a high rate of clinical follow-up could be achieved, angiographic follow-up was not mandatory, which could have led to an underestimation of silent restenosis.

Conclusions

The DEBATE study indicates that it might be feasible, safe, and effective to use DCB for the treatment of patients with de novo lesions in vessels with diameters exceeding 3.0 mm. The incidences of adverse clinical events were low at mid-term follow-up, indicating that Sequent® Please DCB may be considered as a good alternative for patients with large vessel diseases. In this real-world population, mild to moderate dissection post DCB only angioplasty was associated with a benign clinical course.

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Author contributions All of the authors have read and approved the manuscript.

Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

Ethical approval This study was approved by the local ethics committee of our institution.

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