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ORIGINAL PAPER

Drug-coated balloon versus drug-eluting stent in small coronary artery lesions: angiographic analysis from the BASKET-SMALL 2 trial

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Abstract

Background The randomized BASKET-SMALL 2 trial showed non-inferiority for treatment with drug-coated balloon (DCB) compared with drug-eluting stents (DES) in patients undergoing percutaneous coronary intervention (PCI) for de novo lesions in small coronary arteries regarding clinical endpoints at 1 year. In this predefined substudy, we investigated the angiographic findings in patients undergoing a clinically indicated follow-up angiography during the study phase.

Methods Eight-hundred and eighty-three patients underwent PCI with either DES or DCB in a culprit vessel < 3 mm in diameter for stable coronary artery disease or acute coronary syndrome. Event-driven re-angiographies and the corresponding images at baseline were analyzed for angiographic endpoints.

Results One-hundred and eleven patients (117 lesions, 66 DES versus 51 DCB) presented for an unscheduled re-angiography at median 5.7 months after the index procedure. At baseline, mean reference vessel diameter was 2.05 mm and the residual in-segment stenosis after the index procedure was less in DES compared to DCB (23.7% vs 33.8%, $p = 0.001$). At follow-up angiography, diameter stenosis in the DES group (29.0%) was still somewhat smaller than after DCB angioplasty (35.8%) when adjusting for time since PCI ($p = 0.047$), whereas lumen loss (LL) did not differ between the two treatment arms (LL-DES 0.06 mm vs LL-DCB 0.10 mm, $p = 0.20$). Eight patients following DES implantation presented with a complete occlusion of the target lesion compared to no occlusion in the DCB group ($p = 0.009$).

Conclusions The clinically indicated follow-up angiography within 1 year showed no difference in LL. Complete thrombotic vessel occlusions were found only in the DES group.

Clinical Trial Registration www.clinicaltrials.gov; number, NCT01574534

Keywords Percutaneous coronary intervention · Small vessel disease · De novo · Drug-eluting balloon · Drug-coated balloon · Quantitative coronary analysis

Abbreviations

DES Drug-eluting stent
DCB Drug-coated balloon

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SVD	Small vessel disease
PCI	Percutaneous coronary intervention
ACS	Acute coronary syndrome
DAPT	Dual antiplatelet therapy
QCA	Quantitative coronary angiography
LL	Lumen loss
MLD	Minimal lumen diameter
RVD	Reference vessel diameter
DS	Diameter stenosis

Introduction

Drug-eluting stents (DES) are an established treatment option for percutaneous intervention in coronary artery disease, but the use of DES in small coronary arteries is associated with a higher risk of restenosis and lesion failure than in larger vessels [1]. Small vessel disease (SVD) is common among patients undergoing percutaneous coronary intervention (PCI) and has been described in up to 30% of cases.

Drug-coated balloon (DCB) are semi-compliant balloons covered with an anti-proliferative drug such as paclitaxel. During a single balloon inflation, the lipophilic paclitaxel is delivered to the vessel wall surface providing a prolonged antiproliferative effect, and preventing neointimal hyperplasia and lumen loss (LL), without the limitation of permanent vascular implants [2, 3].

The multi-center Basel Kosten Effektivitäts Trial: Drug-Coated Balloon versus Drug-Eluting Stents in Small Vessel Interventions (BASKET-SMALL 2) trial was the first trial powered to assess for clinical endpoints in patients undergoing PCI for de novo lesions in small coronary arteries randomized to DCB or DES [4]. Treatment with paclitaxel–iopromide-coated balloons was non-inferior compared with a treatment with paclitaxel- or everolimus-eluting stents in terms of cardiovascular death, myocardial infarction or target vessel revascularization at 1 year.

Angiographic data following a treatment with DCB and DES in SVD are sparse, especially in a population including acute coronary syndrome (ACS) and treated with new generation stents. Furthermore, several randomized studies investigated the efficacy of DCB compared to DES on scheduled angiographic endpoints, however, these angiographic findings have little clinical implications [5–7].

The aim of this predefined substudy from the BASKET-SMALL 2 trial was to examine and describe the angiographic findings in patients undergoing an unscheduled clinically indicated follow-up angiography during the study phase.

Methods

Study design

The BASKET-SMALL 2 trial was an investigator-initiated, randomized, open-label trial performed at 14 European centers. Patients with stable coronary artery disease or in the clinical setting of an ACS, admitted for PCI in a culprit vessel with a reverence diameter between 2 and 3 mm by visual estimation were prospectively considered for enrolment (Fig. 1). Exclusion criteria comprised concomitant intervention in the same epicardial coronary artery with a diameter ≥ 3 mm, intervention of in-stent restenosis, life expectancy of less than 1 year, or inability to give informed consent.

All patients provided written informed consent. In urgent cases, when the intervention could not be postponed, witnessed verbal assent was obtained from eligible patients in the cardiac catheterization laboratory, and written informed consent was obtained thereafter. The local ethics committee at each participating center approved the protocol and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The sponsor had no role in the design of the study, collection of the data, analysis of the result, in the decision to publish, or in the preparation of the manuscript.

Interventional procedure and randomization

During the coronary intervention, adherence to the recommendations of the European Consensus Group on how to use DCBs in native coronary artery disease was strongly recommended [8]. Special emphasis was paid to an optimal lesion preparation prior to randomization for DCB or DES. Predilatation with an uncoated balloon with a balloon-to-vessel ratio of 0.8–1.0 and inflation pressure exceeding nominal pressure was compulsory.

Randomization in a 1:1 ratio to receive either angioplasty with DCB or implantation of a DES was only done in the absence of a high-grade dissection (type C to F according to the National Heart, Lung, and Blood Institute (NHLBI) classification [8]) and significant vessel recoil of more than 30%. Study participants entered a registry if predilation was not successful and treatment with a bail-out stent was required.

The length of the DCB was chosen to exceed the lesion for at least 2–3 mm on either side. DCB devices were matched according to the reference vessel diameter and recommended inflation time was at least 30 s allowing adequate drug transfer [8]. Investigators were advised to

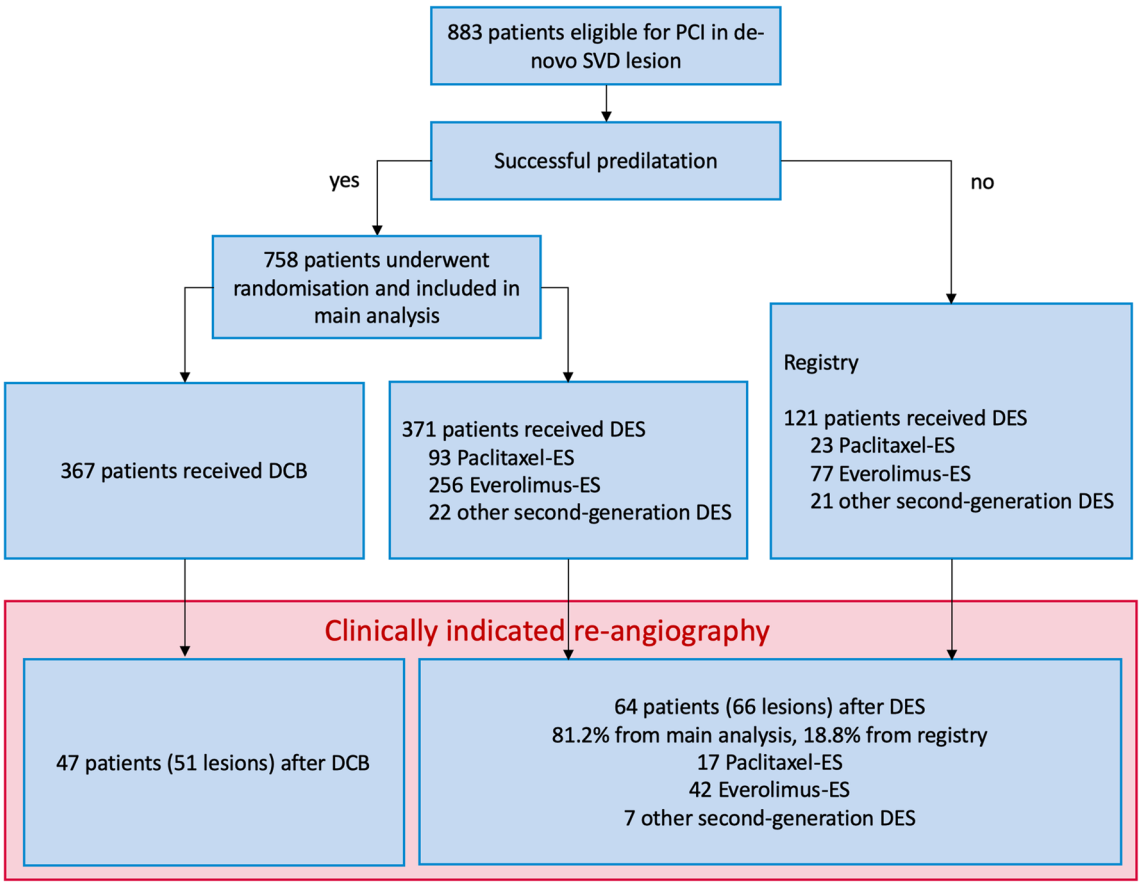


Fig. 1 Patient flow chart. Flow chart showing patients flow and follow-up during the study (*SVD* small vessel disease, *DCB* drug-coated balloon, *DES* drug-eluting stent, *ES* eluting stent)

implant an additional stent after DCB intervention only in case of a flow limiting dissection or a relevant vessel recoil. In case of treatment of more than one target lesion, the randomly allocated treatment had to remain the same for all lesions.

Patients were on dual antiplatelet therapy (DAPT) at the time of the procedure, treated with acetylsalicylic acid and either clopidogrel, ticagrelor or prasugrel following clinical indication according to the most current guidelines of the European Society of Cardiology. In patients with stable coronary artery disease, clopidogrel was also provided for 4 weeks in the DCB-only group, and 6 months when stenting was performed. Recommended DAPT duration following an ACS was 12 months for all participants. In patients on oral anticoagulation, we followed the most current guidelines of the European Society of Cardiology, irrespective of interventional treatment.

Study devices

Patients randomized to the DCB arm were treated with the paclitaxel–iopromide-coated SeQuent Please® balloon (B. Braun Melsungen AG, Berlin, Germany). During the early phase of enrolment, the paclitaxel-eluting Taxus Element® stent (Boston Scientific, Natick, MA, USA) was used but had to be changed to the everolimus-eluting Xience® stent (Abbott Vascular, Santa Clara, CA, USA), since the initial stent was no longer available (Fig. 1).

Follow-up and quantitative coronary angiography

In this analysis, we examined the clinically indicated follow-up angiographies within the 1st year after inclusion and the corresponding images at the index procedure for angiographic outcome (in patients from the main trial and registry). The decision to repeat the coronary angiography was left to the treating physician based on clinical indications. Control angiographies without a clinical indication were not permitted according the protocol. Subsequent angiograms were only used for analysis if no PCI was performed in the target vessel in the meantime.

Each angiogram including quantitative coronary angiography (QCA) was analyzed by trained personnel and reviewed by a radiologically qualified specialist for

cardiology, with both blinded to clinical history. Cases of disagreement were discussed and resolved by consensus. These analyses were undertaken at an independent core laboratory (coreLab Black Forest, Bad Krozingen, Germany) using a state-of-the-art software platform (MEDIS-QAngio-XA 7.3.96.0).

Minimal lumen diameter (MLD), reference vessel diameter (RVD), and percent diameter stenosis (DS) (the difference between RVD and MLD divided by RVD) were analyzed at baseline, post-procedure, and follow-up. All parameters were assessed both in-stent and in-segment (stent plus 5 mm at either end) as previously described [5–7]. In patients treated with a DCB, in-stent referred to the in-balloon measurement, whereas in-segment was defined as the segment treated with the DCB including 5 mm proximal and distal from the edge. LL is defined as the difference between MLD immediately after the procedure and at angiographic follow-up. Net lumen gain reports the difference between the MLD at follow-up and at baseline. Binary angiographic restenosis is defined as stenosis of ≥ 50% of the luminal diameter within a previously treated section at follow-up angiogram. Lesion classification type according to the modified ACC/AHA classification and angiographic calcification grade 0–2 were analyzed from the index procedure angiogram. At the follow-up angiography, thrombus burden was graded from 0 to 5 by the thrombus score, as previously described [9]. Coronary artery dissections after the index intervention and at the follow-up angiography were reported according to the definition of NHLBI classification system for intimal tears, developed by the Coronary Angioplasty Registry [8].

Study objectives

The objective of this predefined sub-study from the BASKET-SMALL 2 trial was to investigate and compare the rate of restenosis, focusing on in-segment LL, between patients treated with DCB and DES in SVD, who presented to a re-angiography during the study phase of 1 year.

Statistical analysis

The unit of analysis is lesion, and outcomes are analysed as per the last re-angiography each patient underwent. We summarize baseline characteristics and raw values of focal variables via descriptive statistics. We compare baseline characteristics between study arms using *t* tests for continuous, and Fisher's exact tests for categorical variables. Comparisons of raw focal variable data between study arms use Wilcoxon's rank-sum tests due to the presence of outliers. For the main comparison of focal variables between treatment arms, we used implemented robust regression models with MM estimation that play down the effect of potential outliers as observed in the data [10]. All models are adjusted for time from PCI to re-angiography centered on the median time. We tested for differences in measurements between predefined subgroups by including the subgroup identifier in models. We tested the interaction term between the subgroup identifier and treatment arm, and followed by a within-group analysis. We report estimates of the difference between study arms alongside 95% confidence intervals. All analyses are performed using R version 3.5.2 [11].

Results

Baseline characteristics

Eight-hundred and eighty-three patients were enrolled in the BASKET-SMALL 2 study (randomized trial and registry) from April 2012 until February 2017 of whom 111 patients (117 lesions) recurred for an event-driven follow-up angiography (Fig. 1). Among those, 66 of the lesions were initially treated with a DES and 51 with a DCB, respectively. The distribution of stent type is summarized in Fig. 1. Clinical and angiographic baseline characteristics were well balanced except for a slightly higher incidence of current smokers and history of previous myocardial infarction in the DCB group (Table 1). Mean age was 67 years and 75% were male. The incidence of diabetes mellitus was high in both groups (36% in DES and 34% in DCB, $p = 0.96$). More than 30% of the patients presented with an ACS at the index procedure. Moderate and severe lesion calcification were described in 36.9% and 31.3% in the DES and DCB group, respectively ($p = 0.49$). The baseline procedural characteristics are reported in Table 2. Predilatation was mandatory according to the protocol and was performed at a pressure of 12.7 atm (± 3.2) and 13.2 atm (± 3.4) in the DES and DCB group, respectively ($p = 0.36$).

According to the QCA analysis at baseline, the average reference vessel diameter was 2.05 mm (2.02 mm (± 0.23) in DES group and 2.08 mm (± 0.31) in DCB group ($p = 0.28$) as shown in Table 3). The residual in-segment DS in the DES group was 23.7% (± 17.8) compared to 33.8% (± 11.7) in the DCB group ($p = 0.001$).

Angiographic outcome at follow-up

A clinical event leading to the analyzed follow-up angiography occurred in median 5.7 months after the index procedure (DES 175 days (77–224), DCB 170 days (82–229), $p = 0.59$). The clinical presentation and angiographic findings are reported in Table 4. We found that DS was still smaller in the stented group compared with balloon group (Estimate 7.18%, 95% CI 0.08–14.28, $p = 0.047$), but the difference in DS tended to be less compared with the difference

Table 1 Baseline clinical and lesion characteristics

	DES	DCB	*p* value
Patients	64	47	
Age (years)	66.6 (11.3)	68.1 (9.4)	0.45
Male sex	45 (70.3)	38 (80.9)	0.27
Diabetes mellitus	23 (36.0)	16 (34.0)	0.96
Insulin-dependent	12 (18.8)	9 (19.1)	
Hypertension	57 (89.1)	39 (83.0)	0.41
Dyslipidaemia	53 (84.1)	38 (80.9)	0.80
Smoking	30 (46.8)	33 (70.2)	0.02
Current smoker	7 (10.9)	14 (29.8)	
Former smoker	23 (35.9)	19 (40.4)	
Family history of CAD	33 (52.4)	14 (33.3)	0.07
Previous myocardial infarction	16 (25.0)	21 (44.7)	0.04
Previous PCI	38 (59.4)	25 (53.2)	0.56
Acute coronary syndrome	22 (34.4)	14 (29.8)	0.64
STEMI	0	1 (2.1)	
NSTEMI	10 (15.6)	7 (14.9)	
Unstable angina	12 (18.8)	6 (12.8)	
Renal failure	13 (20.3)	11 (23.4)	0.82
Multivessel disease	51 (79.7)	36 (76.6)	0.88
Two-vessel disease	18 (28.1)	14 (29.8)	
Three-vessel disease	33 (51.6)	22 (46.8)	
Lesions	66	51	
Target vessel			0.90
Left anterior descending	9 (13.6)	8 (15.7)	
Diagonal	11 (16.7)	8 (15.7)	
Left circumflex	32 (48.5)	26 (51.0)	
Right coronary artery	4 (6.1)	1 (2.0)	
PDA or PLA	10 (15.2)	8 (15.7)	
Lesion type			0.51
B1	30 (45.5)	28 (54.9)	
B2	13 (19.7)	6 (11.8)	
C	5 (7.6)	2 (3.9)	
Lesion calcification			0.49
Moderate	21 (32.3)	12 (23.5)	
Severe	3 (4.6)	4 (7.8)	

Values are mean (±SD) or *n* (%). *p* values from *t* tests for continuous variables and Fisher's exact tests for categorical variables

DES drug-eluting stent, *DCB* drug-coated balloon, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-segment elevation myocardial infarction, *PDA* posterior descending artery, *PLA* posterolateral artery

observed directly after the index PCI. LL tended to increase over time in both groups, however not showing any difference in increase rate between the two treatment arms (interaction test between treatment arm and time to reangiography, $p=0.36$). We found no statistical support for a difference in LL between treatment arms (Estimate 95% CI 0.09 (− 0.05 to 0.23), $p=0.20$, Fig. 2).

Table 2 Baseline procedural characteristics

	DES ($n=66$)	DCB ($n=51$)	*p* value
Pressure for predilatation (atm)	12.7 (3.2)	13.2 (3.4)	0.36
DES			
Diameter (mm)	2.54 (0.24)		
Length (mm)	19.5 (10.2)		
High-pressure post-dilatation	39 (59.1)		
DCB			
Diameter (mm)		2.54 (0.35)	
Length (mm)		23.0 (7.4)	
Duration of inflation (s)		55.6 (23.0)	

Values are mean (±SD) or *n* (%), high-pressure dilatation with > 12 atm

Atm atmosphere, other abbreviations as in Table 1

A visual representation of these results via boxplots and the empirical cumulative distribution function of LL is offered in Fig. 3a, b. We see that the cumulative frequency distribution of LL was similar between treatment arms up to 0.5 mm, while larger LL was observed more frequently in the DES group.

Complete thrombotic vessel occlusion

A striking observation in Fig. 3a is the presence of eight patients who presented with a complete thrombotic vessel occlusion after undergoing stent implantation compared to none after a DCB intervention (Fisher's exact test $p=0.009$). The detailed information on this patient group with stent thrombosis is reported in the Supplementary Table 1. Reference vessel diameter reached from 1.79 to 2.21 mm, which is in the range of the overall study population. The occlusion occurred as acute stent thrombosis within 24 h up to 335 days after the index procedure. None of the lesions had a severe vessel calcification, and lesion classification type reached from A to C. Seven patients presented with an ACS (3xSTEMI, 1xNon-STEMI, 3xunstable angina) and one patient with symptoms of heart failure. Thrombotic stent occlusion occurred in seven patients despite a prescribed concomitant treatment with DAPT, in one patient stent thrombosis emerged after planned cessation of clopidogrel after 6 months.

Fate of dissection after DCB angioplasty

After DCB angioplasty, 12 patients were left with a persistent coronary dissection (three type A, eight type B, one type C). At the follow-up angiography, complete vessel healing was observed in nine patients (75%). Of note, the three residual dissections were all observed on the re-angiographies

Table 3 Quantitative coronary angiography measurements at baseline and after the procedure

	DES ($n=66$)	DCB ($n=51$)	p value
Baseline			
Reference vessel diameter (mm)	2.02 (0.23)	2.08 (0.31)	0.28
Minimal lumen diameter (mm)	0.51 (0.27)	0.61 (0.35)	0.08
Diameter stenosis (%)	75.0 (12.3)	70.0 (13.5)	0.04
Length (mm)	11.4 (8.8)	11.2 (6.0)	0.90
Post-procedure			
Minimal lumen diameter (mm)			
In-segment	1.53 (0.34)	1.36 (0.23)	0.004
In-stent/in-balloon	1.83 (0.29)	1.48 (0.25)	< 0.001
Diameter stenosis (%)			
In-segment	23.7 (17.8)	33.8 (11.7)	0.001
In-stent/in-balloon	8.8 (15.7)	27.72 (15.0)	< 0.001
Acute gain (mm)			
In-segment	1.02 (0.42)	0.75 (0.34)	< 0.001
In-stent/in-balloon	1.32 (0.35)	0.87 (0.38)	< 0.001

Values are mean (± SD). p values from t tests (abbreviations as in Table 1)

Table 4 Clinical presentation and angiographic outcome at follow-up

	DES	DCB	Estimate (95% CI)	p value
Patients (n)	64	47		
Time until follow-up (days)	175 (77–224)	170 (82–229)		0.70
Clinical presentation (n)				
STEMI or NSTEMI	13 (20.3)	6 (12.8)		0.32
TVR	7 (53.8)	3 (50.0)		
UA or stable CAD	49 (76.6)	40 (85.1)		0.34
TVR	13 (26.5)	10 (25.0)		
Other	2 (3.1)	1 (2.1)		~ 1
Lesions (n)	66	51		
Minimal diameter (mm)				
In-segment	1.49 (1.26 to 1.76)	1.27 (1.12 to 1.52)	− 0.19 (− 0.38 to 0.00)	0.048
In-stent/in-balloon	1.76 (1.47 to 2.02)	1.35 (1.13 to 1.70)	− 0.35 (− 0.54 to 0.17)	< 0.001
Diameter stenosis (%)				
In-segment	29.0 (20.3 to 45.5)	35.8 (24.8 to 44.9)	7.18 (0.08 to 14.28)	0.047
In-stent/in-balloon	18.8 (9.6 to 35.8)	34.5 (19.1 to 42.8)	14.7 (7.7 to 21.6)	< 0.001
Lumen loss (mm)				
In-segment	0.06 (− 0.15 to 0.40)	0.10 (− 0.14 to 0.26)	0.09 (− 0.05 to 0.23)	0.20
In-stent/in-balloon	0.13 (− 0.14 to 0.57)	0.10 (− 0.16 to 0.34)	0.03 (− 0.13 to 0.19)	0.72
Net gain (mm)				
In-segment	1.40 (0.75 to 1.89)	1.18 (0.89 to 1.59)	− 0.29 (− 0.56 to 0.01)	0.045
In-stent/in-balloon	1.46 (0.93 to 2.08)	1.24 (0.84 to 1.86)	− 0.39 (− 0.70 to 0.09)	0.011
Binary restenosis (n)			OR	
In-segment	14 (21.5)	10 (20.4)	0.91 (0.35 to 2.25)	0.83
In-stent/in-balloon	12 (18.5)	8 (16.3)	1.01 (1.00 to 1− 03)	0.66

Values are median (IQR) or n (%). p values from robust regression models (logistic regression for binary restenosis) adjusting for time to reangiography

CI confidence interval, *TVR* target vessel revascularisation, *OR* odds ratio, other abbreviations as in Table 1

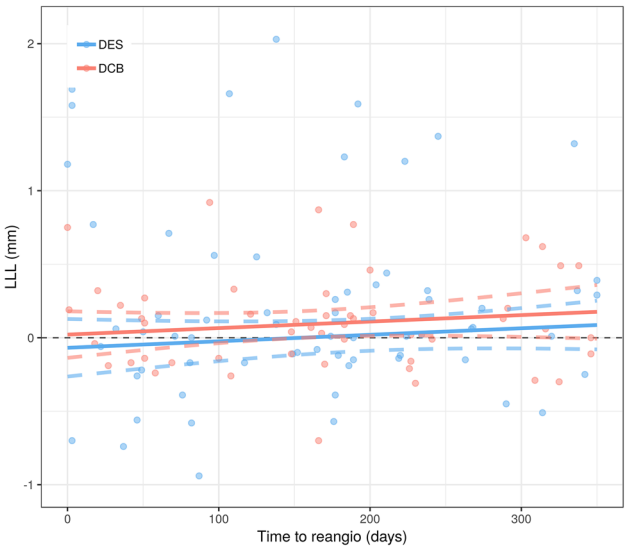


Fig. 2 Lumen loss by time. Lines show the predicted LL over time and their 95% confidence intervals (dashed) (abbreviations as in Fig. 1)

within only 7 weeks (day 0, 18 and 51, respectively), with no residual dissection reported thereafter. The three patients that had an unhealed coronary dissection had two type A and one type B dissection after the index PCI, which remained unchanged at the follow-up angiography.

Subgroup analysis of angiographic outcome

The results of formal interaction testing, which was conducted to assess whether in-segment late loss was consistent among important subgroups, as shown in the Supplementary Table 2. We found no evidence for LL to differ between treatment arms according to subgroups. Only for the effect of diabetes, we found weak evidence of a potential interactive effect, with larger LL in DCB versus DES for non-diabetic, but no effect of treatment on LL in diabetic patients (interaction $p = 0.047$).

Discussion

In this predefined substudy of the BASKET-SMALL 2 trial, we examined angiographic measurements between treatment arms in patients with a clinically indicated follow-up angiography. We found no evidence for a difference in LL between study arms, and only weak evidence for a difference in DS in favor of the stent. However, eight patients from the DES arm, compared with none from the DCB arm, were found with a complete thrombotic occlusion in the target lesion.

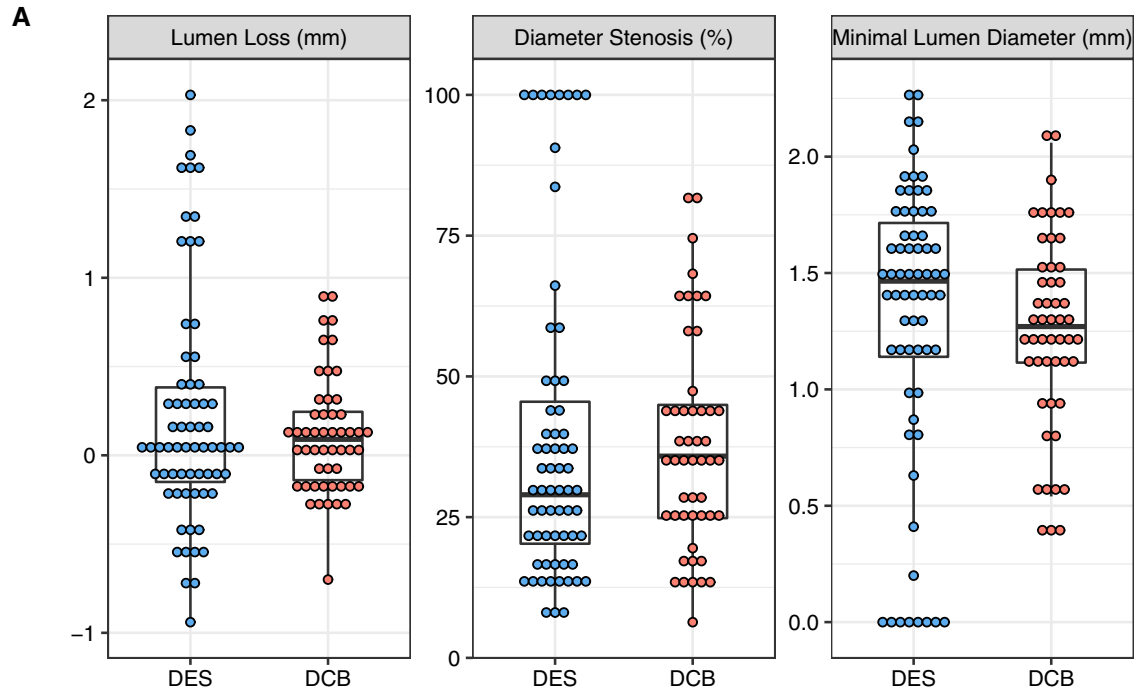
Lumen loss

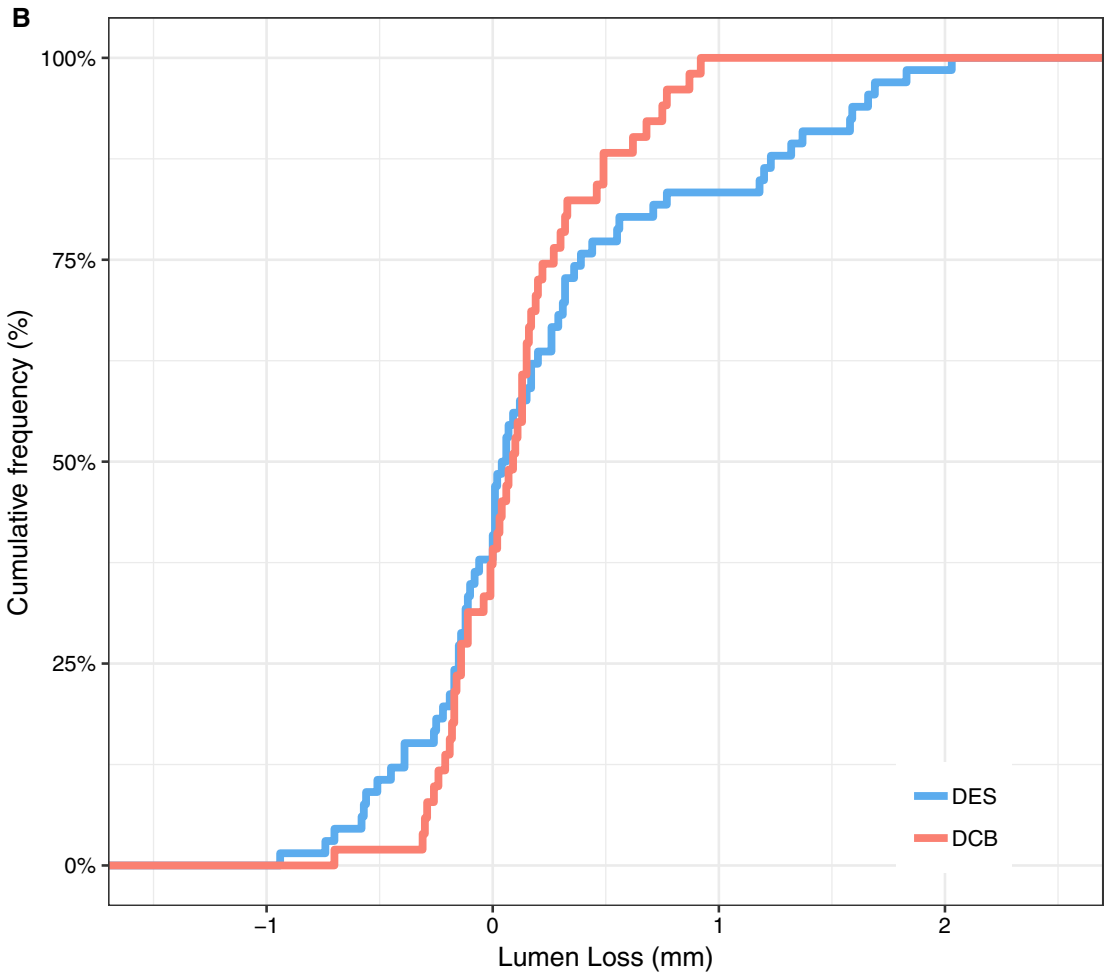
The presence of metallic implants interferes with vessel healing processes and may cause chronic neointimal hyperplasia and neoatherosclerosis, which is the morphological explanation for in-stent restenosis [12]. Restenosis is more common in smaller arteries due to their limited capacity to accommodate neointimal hyperplasia. To overcome the remaining obstacles of durable metallic stents, DCB were developed to allow PCI without foreign body-associated drawbacks [13] and without permanently caging the vessel (might interfere with vessel remodeling and vasomotion) [14, 15].

In the BELLO trial, DCB overcame first-generation DES in terms of the primary endpoint of in-stent/in-balloon LL at 6 months for the treatment of de novo SVD [6]. The RESTORE SVD China trial, comparing the angiographic endpoints of a DCB intervention with those of a second-generation DES implantation in patients with small native coronary artery disease, showed a non-inferiority of DCB compared with DES for the primary endpoint of angiographic in-segment DS at 9 months [7].

In our study population, although we saw a clear difference in in-segment DS in favor of the DES directly after the index procedure, when examined at the time of the clinically indicated re-angiography this difference was smaller and received only weak statistical support. However, we did not find statistical support for a difference in LL between the two groups.

Our quantitative angiographic results are in line with the findings reported in the aforementioned trials, but comparing these studies is difficult due to their different study designs. On one hand, the investigators from the BELLO trial used only first-generation stents as comparator, reported a 20% treatment cross-over in an intention-to-treat analysis, and focused their primary endpoint on the in-stent/in-balloon measurement (a metal scaffold with a high radial force has the ability to overexpand a lesion as reported with the in-stent/in-balloon measurement, however restenosis may occur just proximal and distal from the stent, which still compromises the coronary flow in the vessel. Therefore, the assessment of in-segment measurement seems more appropriate from a clinical perspective [6]. On the other hand, RESTORE SVD China used newest-generation DES as comparator in all patients with a follow-up of 9 months [7]. Finally, our patients presented to a clinically indicated re-angiography, rather than to a scheduled follow-up. The aim of our descriptive observational study was to assess angiographic findings on event driven re-angiographies, which allows to look for evidence with a potential clinical consequence, as opposed to routinely collated data. These angiographical findings were in line with the equipoise clinical outcome of the original BASKET-SMALL 2 study [4].


A
Lumen Loss (mm)
Diameter Stenosis (%)
Minimal Lumen Diameter (mm)
DES
DCB


B
Cumulative frequency (%)
100%
75%
50%
25%
0%
Lumen Loss (mm)
DES
DCB

◂**Fig. 3** **a** Box plots. Box plots showing median levels (IQR) of in-segment late lumen loss, diameter stenosis, and minimal lumen diameter at follow-up angiography (abbreviations as in Fig. 1). **b** Lumen loss distribution. Cumulative frequency distribution curves of in-segment late loss at follow-up angiography (abbreviations as in Fig. 1)

Since patients in our study presented at different time points to the follow-up angiography, the development of restenosis was investigated along time. The mechanisms of LL differ between the stent and balloon group. In-stent restenosis is a course of smooth muscle cell migration and proliferation as a reaction to the stent platform and its polymeric matrix, whereas restenosis after balloon angioplasty is a sequence of early vessel recoil, later vascular remodeling and to a lesser extent cell proliferation [16]. Neointimal cell proliferation is a continuous and slow development, suggesting that sustained local drug application is required for its effective inhibition. However, DES are characterized by sustained drug delivery only up to a few months, leaving a "bare-metal stent" behind that could induce continuous inflammation and intimal cell proliferation. We found a small tendency for LL to increase along time, at a rate that did not differ between study groups despite the aforementioned pathophysiology of restenosis development. Of note, patients treated with a bioresorbable vascular scaffolds in small coronary vessels, a late positive vascular remodeling was shown after initial LL [17]. Bioresorbable scaffolds lead to the expected LL in the first 6 months, though, with progressing scaffold absorption a lumen increase develops from month 6 to 24. This suggests that it is unlikely to find a decrease in LL within 1 year after an initial vessel injury by DCB, compared with new-generation DES. This hypothesis is also strengthened by the clinical long-term result from the BELLO trial, not showing a long-term benefit of DCB over permanently implanted stents until 2–5 years after the initial intervention [18].

Complete vessel occlusion

The finding potentially having the biggest impact on clinical practice is that complete vessel occlusions were only found in patients after stent implantation, compared to none in the DCB group. The BASKET-SMALL 2 trial was by far the largest prospective study in SVD investigating a treatment with DCB compared with DES on clinical endpoints, and therefore offering sufficiently a large number of patients to assess for an endpoint such as acute vessel occlusion.

Our results are in line with the findings reported by Venetsanos et al. who analyzed the Swedish Coronary and Angioplasty Registry (SCAAR) for patients undergoing PCI with either DES or DCB in all-sized vessel for the endpoint of definite target lesion thrombosis [19]. In this propensity matched cohort including 1197 new-generation DES and 1197 DCB, at a mean follow-up of 2.5 years, the cumulative incidence of target lesion thrombosis was 1.1% versus 0.2% (adjusted HR 0.18; 95% CI 0.04–0.82), respectively. We explain the even higher rate of stent occlusions in our population with a smaller vessel diameter. After stenting with DES, the majority of the vascular wall is not covered by the stent struts. To ensure antiproliferative efficacy in the treated segments, high concentrations of an antirestenotic drug is needed, with the consequence of incomplete and delayed endothelialization of the stent struts. This late re-endothelialization in combination with a small vessel diameter seems to provoke thrombotic occlusion more than in all other reported DES trials in large coronary vessels [20].

In our eight patients suffering a stent occlusion, one event occurred after guideline compliant cessation of the DAPT. This raises the question whether patients undergoing stenting of a small coronary artery should in fact receive a prolonged DAPT. At least in patients with a high bleeding risk, where prolonged DAPT is contraindicated, an intervention with DCB should be considered as the preferred treatment of SVD.

Fate of coronary dissection

Proper lesion preparation is essential in the use of DCB angioplasty. The disappointing performance of the first-generation DCB, as reported in the PICCOLETO trial, might have been related to insufficient lesion preparation, where predilatation was done in only 25% [5]. In this present study, lesion preparation was mandatory according to the protocol and was undertaken with an average inflation pressure of 13 atm. However, aggressive lesion preparation may lead to severe coronary dissections. An observational study by Cortese et al. demonstrated in patients with minor dissections (A–C dissections according NHLBI classification) following a coronary intervention with DCB of de-novo coronary lesions that a conservative approach in combination with a potent antiplatelet regime is accompanied by a high chance of complete vessel healing at 6 months and rarely causes relevant clinical events [21].

Our study is in line with these results, since complete vessel healing was observed in 9 of the 12 patients left with a persistent coronary dissection after the index DCB angioplasty. The three residual dissections at the follow-up angiography were all observed at a very early timepoint and remained the same compared with the initial observation. There were no residual dissections found in an angiography after 7 weeks. Furthermore, the BASKET-SMALL 2 trial reported no acute vessel occlusion at the index procedure. This outcome furthermore underscores the safety profile of a DCB approach in the setting of SVD intervention.

Limitations

This study should be interpreted in view of the following limitations. First, we also incorporated results derived from the BASKET-SMALL 2 registry after bail-out stenting, which may cause a selection bias for the stent group. However, the numbers of patients from the registry were small (18.8% from the DES group), the baseline characteristics were still well balanced, the reason for bail-out stenting was a balloon-induced coronary dissection or vessel recoil (rather than comorbidities), and the observed stent thrombosis was found in only two patients from the registry compared to six patients from the main analysis (see supplementary appendix for detailed patient information). Second, the number of patients is rather small. And yet, this is the largest prospectively collected cohort of patients presenting after PCI in SVD with a clinical indication for a re-angiography and therefore with a potential clinical consequence (rather than routinely collected data for a surrogate endpoints). Finally, the observation time of 1 year is fairly short. Longer-term data from the BASKET-SMALL 2 trial are awaited.

Conclusion

Patients from the BASKET-SMALL 2 trial treatment with either DCB or DES for small vessel coronary disease showed no evidence for difference in LL on a clinically indicated follow-up angiography within 1 year. Eight patients presented with a complete thrombotic occlusion of the target lesion after DES intervention, compared to no occlusion in the DCB group.

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Compliance with ethical standards

Conflict of interest Dr. Jeger reports Grants from Swiss National Foundation, Grants from Basel Cardiovascular Research Foundation, Grants, personal fees and non-financial support from B. Braun Medical AG, Sempach, Switzerland during the conduct of the study; Dr. Mangner reports personal fees from Edwards Lifesciences, personal fees from Medtronic, personal fees from Biotronik, personal fees from Sanofi Genzyme, personal fees from Astra Zeneca and personal fees from Novartis outside the submitted work; Dr. Scheller reports other support from B.Braun, InnoRa GmbH and Charite University Hospital outside the submitted work; Dr. Twerenbold reports personal fees from Abbott, Roche, Siemens, Brahms, Singulex and Amgen, Grants from Swiss National Science Foundation, Swiss Heart Foundation, Swiss Society of Cardiology, University of Basel and Cardiovascular Research Foundation Basel outside the submitted work; all the other authors have nothing to disclose.

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